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Part I.—Original Articles.

EXCITATORY ABREACTION: WITH SPECIAL REFERENCE TO ITS MECHANISM AND THE USE OF ETHER.

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THE origin of the term abreaction dates from the time of Breuer and Freud's (1) early studies in hysteria, when they observed that patients were helped by "just talking it out." Later their technique was employed under hypnosis (2). Sadler (3) defined abreaction as "a process of reviving the memory of a repressed unpleasant experience and expressing in speech and action the emotions related to it, thereby relieving the personality of its influence." Miller (4) quotes Freud as holding that experiences shall be recalled with emotional vividness. "Affectless memories are almost useless," said Freud.

Freud himself soon abandoned this hypnotic method of abreaction in favour of free association and the psychoanalytical technique. However, during the First World War it became apparent that abreaction had a very definite place in the treatment of acute "traumatic neuroses" (5). Millais Culpin (6) stated, "Once the man's conscious resistance to discussing his war experience was overcome, great mental relief followed the pouring out of emotionally charged incidents. It was as if the emotion pent up by this conscious resistance had by its tension given rise to symptoms. The memory, usually of a nature unsuspected by me, then came to the surface, its return being preceded perhaps by congestion of the face, pressing of the hands to the face, tremblings, and other bodily signs of emotion." William Brown (7) pointed out in 1920 that the improvement was often solely dependent on the abreaction obtained and

not on suggestion. "Suggestion removes the symptom, abreaction removes the cause of the symptom by producing fully adequate re-association."

As previously indicated by Freud, Millais Culpin (8) stressed, from his experiences in treating traumatic neuroses, that an incident may be remembered, but the emotional content may be separated from it and repressed. Thus with the passage of time the word abreaction has taken on a wider and more elastic significance, including the reliving with affect of conscious and unconscious material. In fact it is in this wider sense that we use the term in this paper.

Between the two World Wars the lessons of abreaction were largely forgotten, but a new approach was opened by the introduction of the use of barbiturates in psychotherapy by Blackwenn (9) in America in 1929. Lindemann (10) and Wagner (11) using sodium amytal and Stockert (12) and Campbell (13) using sodium evipan were a few of the pioneers in this field. Horsley (14) in 1936 elaborated the method of employing intravenous nembutal or pentothal to facilitate discharge of repressed emotion and memories while the patient was in a suggestible state induced by the drug. This method was only slowly adopted by psychotherapists, but in 1940 Sargant and Slater (15) reported on its value in the treatment of the acute Dunkirk casualties, among whom were a very high proportion of cases with gross conversion symptoms, particularly amnesias (16). Discussing their findings in this group, Debenham, Hill, Slater and Sargant (17) advised that under the barbiturate the patient should be encouraged to "re-experience the violent emotions that battle scenes have aroused."

Following these reports, drug abreaction became widely adopted in the treatment of military casualties in Great Britain. Further interest was stimulated among American workers by Grinker and Spiegel's (18) use of this technique in North Africa in 1942, though some confusion was added by the adoption of yet another name, "narcosynthesis." At the same time Palmer (19) was achieving interesting results by employing ether instead of a barbiturate. Still later Rogerson (20) substituted nitrous oxide.

It is the intention of this paper to discuss some of our findings in the abreaction of patients with ether, which we started to use in 1944, following the method developed by Palmer. It is, however, worthy of note that Hurst and his collaborators (21) made use of "etherization" in the treatment of hysterical conversion symptoms in the 1914–18 war. His clinical accounts frequently describe the induced excitement, but the method, not specifically recognized as abreaction, was only occasionally used, and generally after firm suggestion or persuasion had failed. Also Penhallow (22) in Boston reported "a case of mutism and deafness due to emotional shock cured by etherization" in 1915. Prior to our use of ether techniques, we had been using barbiturates for four years on a variety of cases among the many thousands who had passed through the unit for treatment during that time. Comparison between the two methods revealed some remarkable differences which led us to speculate and experiment on the whole mechanism of abreaction. The subject has been surrounded for so long by so much psychological theory that certain basic physiological principles may have become obscured.

To arrive at a physiological basis for the use and understanding of abreaction it is first necessary to study the work of experimenters in higher nervous activity. Pavlov's experiments have, despite their limitations, the advantage that they can be repeated and few have been inclined to dispute their accuracy. We therefore wish to recapitulate a few of his findings which we believe are relevant to the problem of abreaction. Just as it is now generally accepted that those who break down even under severe battle stress generally have evidence of constitutional predisposition, so Pavlov found he could divide his dogs into those with ill-balanced nervous systems liable to excessive excitation or inhibition, and those whose nervous systems were with difficulty upset by stimuli, maintaining a steady balance between excitation and inhibition. In 1924 many of Pavlov's dogs were nearly drowned in the Leningrad floods. When rescued at the last moment from their cages, in which they were trapped and swimming about with their heads just above water, some were in a state of acute excitement, which was succeeded by a phase of " collapse " or stupor. This in turn gradually passed off. Pavlov discovered by experiment that this terrifying experience, which had produced great nervous excitement and what he described as " ultraparadoxical " cortical inhibition, had destroyed a series of conditioned responses which he had implanted in these dogs by months of patient work. Other more stable dogs were less affected, did not exhibit such marked excitatory and inhibitory phenomena, and did not lose similar conditioned responses in face of similar psychological trauma. This dramatic extinction of recently acquired conditioned reflexes interested us in relation to the mechanism of abreaction, as also did the fact of its special occurrence in dogs with " weak nervous systems," who were liable to go into cortical transmarginal inhibition under exciting stimuli. For the rest of this paper, when the term transmarginal inhibition is used, we mean the final ultraparadoxical phase of cortical inhibition following an overwhelming stimulus. This may break up recently acquired conditioned behaviour, and is what we wish to suggest may have some relation to the therapeutic value of emotional abreaction in psychotherapeutic techniques.

Pavlov's laws governing the phenomena of nervous excitation and inhibition, their irradiation, concentration and mutual or reciprocal induction, and his demonstration of the " equivalent," " paradoxical " and " ultraparadoxical " phases of inhibitory cortical activity are well known, and can be read in books on conditioned reflexes and their relation to psychiatry (23, 24, 25). He postulates that morbid states of brain activity can be brought about by the collision of excitatory and inhibitory processes, as a result of which a dynamic stereotypy of abnormal behaviour may develop which needs less and less work to sustain it. The normal regulation of excitatory and inhibitory balance may quickly become chaotic, especially in those with unstable nervous systems. Many of the apparently inexplicable behaviour patterns seen in acute war neuroses were faithfully reproduced in Pavlov's dogs under experimental conditions, and are understandable if reference is made to the laws established by Pavlov in twenty years of experimental work. We have discussed this together with some preliminary observations on abreaction in a previous publication (26).

To return to the problem of abreaction. In abreacting patients with ether we immediately noticed a great difference from similar cases we had previously abreacted with barbiturates. Ether produced much more easily a far greater degree of excitement. The same effects were achieved by barbiturates, and by hypnosis for that matter, but the recital of events was usually less intense. Another striking observation is one to which we will refer constantly in this article; that is, the more frequent occurrence of sudden states of "collapse" in the course of an emotional outburst of particular severity when ether is employed. Again this can be obtained under barbiturates or hypnosis, but only occasionally so. We believe the phenomenon corresponds to Pavlov's observation in some of his dogs, that the production of acute excitement leads to a phase of transmarginal inhibition in which the cortex is momentarily incapable of further activity and, as happened in the Leningrad flood, there may result an abolition of recently implanted conditioned behaviour patterns. During abreaction our patients could be made to reach a pitch of terror, anger and excitement, and then suddenly collapse and lie motionless, unmoved by ordinary stimuli for a minute or so. On coming round they would often burst into a flood of tears, or state that outstanding symptoms had gone. A patient might describe his mind as being freed of ideas that had dominated it. He could still think of them, but without associated anxiety or hysterical responses. On several occasions—and this we considered one of our most important observations—when simple excitement at the recital of experiences was produced without a resultant end-stage resembling transmarginal inhibition, little or no improvement occurred. When abreaction was repeated and total inhibition produced by stimulating further excitement, recovery ensued.

Such a technique was not necessary in all types of case. Some cases of recent amnesia, for instance, required but little barbiturate to bring about cortical relaxation, and for a memory then to come flooding back without further effort on the part of the doctor or patient. Ether proved useful for cases in which this was not sufficient. These were the cases in which abnormal behaviour had become more organized and fixed, and had taken on the quality of a stereotypy which needed less and less work to sustain it. Such conditions often became chronic, disabling, persistent, and resistant to simpler measures. But with the massive excitation aroused under ether ending in a transmarginal inhibition, the whole recently built up pattern of behaviour could be disrupted with ensuing rapid recovery.

Pavlov found that some of his dogs were capable of being reconditioned after their experiences in the Leningrad floods, whereas in those with the weakest type of nervous system reconditioning was always unpredictable and sometimes impossible. In the better "inhibitory" type of dog, with the cortical slate wiped clean, the therapist could again write on it. In the weaker animals no stable patterns of behaviour could be re-implanted. The similarity to therapeutic reconditioning in a transference situation enhanced by a dramatic emotional abreaction, in the course of an analysis, is too striking to need further emphasis. It was also exactly what we found in our patients.

Technique of Ether Abreaction.

Ether has proved to be a suitable and useful medium for the facilitation of excitation. Its pharmacological action is to depress the most highly evolved psychic centres first, thus producing disinhibition (27). The amount we administer is far short of the anaesthetic stage, and the open mask method obviates the irritation and suffocating sensations of the closed method, as used in anaesthesia. In this manner it acts as a mild intoxicant and produces a sensation of warmth (the cutaneous and cerebral vessels are dilated), some confusion of thought and loss of self-control. The exhilarating properties of ether have long been known, and the use made of it for pleasurable purposes largely contributed to its discovery as an anaesthetic. Keys (28), in describing its use at parties or "ether frolics," says, "These young participants became pleasantly drunk. They lost their sense of equilibrium, talked foolishly, and sometimes laughed with complete abandon." F. W. Cock (29), in his graphic description of the first operation under ether in Europe (amputation performed by Robert Liston at University College Hospital on 21 December, 1846), relates how a preliminary trial was carried out in the operating theatre on one of the hospital porters, Mr. Sheldrake, before the great Liston arrived. "So the porter lies down on the table and sucks away at the tube, young Squires holding his nose. But after a minute or two, Sheldrake jumps off the table quite intoxicated and making a tremendous to-do, climbs on to the railings and plunges into the mass of students, who are like a flock of sheep when a dog chases it, separating right and left, and letting him nearly reach the door."

There have been numerous accounts of the techniques of abreaction under barbiturates and the methods adopted to stimulate excitement. Roughly the same technique is used with ether; it is essentially simple, but the results depend to a large extent on the experience and personality of the doctor. It is best to warn the patient beforehand that there is no intention whatever of anaesthetizing him or putting him to sleep, as the fear that the "mask treatment" or "ether treatment" is given for such a purpose may diminish the patient's co-operation. We explain to the patient that the treatment is given to allow the freeing and release of emotion or tension that is "locked-up" inside him and giving rise to symptoms. A firm well-padded couch or bed is essential or the patient may hurt himself during his excitement, and it is a wise precaution to have a sufficient number of nurses or doctors present to control the patient. If this is not done, it may be impossible to carry on the abreaction if the patient is violent or struggling and shouting. In powerful muscular individuals some form of mechanical restraint may be an advantage, and in such cases a restraint jacket used in E.C.T. (Sargant and Slater (30)) has proved valuable in the absence of sufficient staff. A Schimmelbusch mask with about 8 layers of gauze is best used, together with an ether drop bottle. The patient lies flat and is first talked to in an informal way about events prior to the onset of his illness, or prior to the incident over which he is to be abreacted. Care should be taken not to drop any ether into the eyes, and a pair of dark goggles is a useful protection. The mask should be sprayed with a liberal quantity of ether from the start, and although held away

from the face during the first few whiffs and the preliminary talk, it should be quickly approximated to the face, except in bronchitic subjects. A preliminary injection of atropine sulphate, gr. $\frac{1}{100}$ is given to the latter type of patient. Soon after the preliminary discussion the patient is brought back to the scene of the breakdown or to a past incident that had been accompanied by much emotional significance. It is important not to administer the ether too slowly nor to use too little at a time, as this method will result in a gradual anaesthetization, with the patient tending to exhibit a prolonged drunken phase in which it is difficult to establish contact with him. If the light etherization (there is no anaesthetization in the accepted sense) is done successfully, the patient usually becomes quickly and wildly excited and begins to abreact. The voice becomes louder, the face reddens, and the flush becomes deeper as the emotional release occurs. Much depends on the way in which the physician handles the situation. Often the trigger stimulus only becomes apparent during the treatment, and one has to be on the alert to seize on this and press it home. The therapist may have to enter into the spirit of the particular situation recalled or created. Thus he may have to shout or whisper, or swear or imitate certain noises as the case may be, and it may well be an exhausting business. With ether the recital of events is often more dramatic than with barbiturates, and the patient is more likely to behave as though those same events were happening now. He is of set purpose encouraged to cry, shout and struggle, as the greater the degree of excitement the better may be the eventual therapeutic result. The onset of excitement from the commencement of treatment varies from about a minute to ten minutes or more. It may be necessary to probe, encourage and coerce, and a case that is seemingly too inhibited to abreact may suddenly do so. The excitement varies in intensity and duration ; some patients keep up a level of excitement for a time, others may quickly stop and appear to become inhibited, but soon resume again, and yet others show a rising pitch of excitement and suddenly fall back at its climax into an inert state. For a few minutes they remain flaccid and quiet, as though felled into unconsciousness. A mixture of fear and released aggression, constantly stimulated by the therapist, produces the most satisfactory terminal emotional collapse.

It is generally easy to produce an emotional release in an individual suffering from a recent acute traumatic neurosis (Kardiner places this group as occurring roughly within a week or two of the precipitating incident), but in a long-standing illness, particularly one in which reactive depression has become a prominent symptom, the patient may have the utmost difficulty in relaxing and reliving the traumatic situations. He tends to answer in the past tense and in an impersonal manner, and some of the emotion displayed does not ring true, i.e. it is done to satisfy the therapist. It is often in these cases that some therapists will succeed in producing a useful abreaction with ether, whereas others will fail. In such cases ether shows its superiority over barbiturates.

After the abreaction and removal of the mask the patient may weep or burst into laughter or alternate between laughter and tears. He is encouraged to talk, and so may perhaps continue the uncovering of an amnesia or relate

further incidents of importance. He frequently volunteers the statement that his mind feels relieved and easier. " Something has lifted " or " My head feels clearer " or " I have lost my tension " are expressions often heard. It is our practice, if very emotional incidents have been revealed and the patient continues to be somewhat excited, to follow the abreaction with sedative or sleep treatment for a day or more, depending on the patient's stability.

Experimental Observations Relating to Excitatory Abreactions.

Our experiences early on in the war, with Dunkirk casualties and those from the London blitz and Battle of Britain in 1940, showed that immediate first-aid sedation, or the injection intravenously of a barbiturate drug, would at once break up many acute hysterical reactions to traumatic experiences and prevent a fixation of abnormal patterns of behaviour. Excitatory abreaction was sometimes necessary, and in recent cases this was fairly easy to produce with barbiturates (17). Anxiety was just below the surface and traumatic memories were fresh. When we experimented with ether in the acute Normandy cases and patients from the V-bomb attacks on London, we investigated more fully acute hysterical reactions that failed to respond to ordinary abreaction or suggestion under barbiturates ; we found some could be more easily helped by the far greater degree of excitation released by ether. Case 1 is a good example of this, but a satisfactory result might also have been obtained had a more deliberate excitatory technique been adopted under barbiturates.

Case 1.—I. U—, male, aged 26, was admitted to hospital in 1945 complaining that he was unable to stop shaking. There was nothing relevant in his family history. He had chorea at the age of 11, and described himself as one who " always worried inwardly," nervous, afraid of the dark and prone to headaches. In the Army he drove Diesel engines loaded with ammunition and was continually frightened by the possibility of an explosion. His home was badly damaged in the Battle of Britain in 1940.

Patient stated that two days before admission he was in his bedroom when a rocket exploded approximately a mile away. He " felt something hit him," heard his wife calling him downstairs, and when he got down he collapsed and was unable to stop shaking. On examination he appeared extremely anxious. There was a very gross tremor of the arms and legs ; the arms moved through a wide angle, and he was unable to walk without support because of the tremor of his legs. His face was anxious and drawn with an expression of distress and his forehead was wrinkled.

Suggestion under intravenous sodium amytal slowed down the jerkings and tremors, but this recurred as soon as the effect of the amytal wore off. A violent abreaction over the bomb incident was then carried out under ether, and a rapid improvement ensued. After a few days' continuous narcosis he was discharged substantially recovered.

It was in patients with good previous personalities showing the more chronic hysterical reactions that ether was found more useful than barbiturates. Such patients were treated at a stage when excitement had given place to lethargy and neurotic patterns had started to become stabilized. There was a tendency for such patients to give a rather dull recital of events under amytal, as it was more difficult for them to relive exciting episodes which had become clouded by subsequent events and symptoms. With the use of ether we began to

obtain more dramatic abreactions more easily. Case 2 is quoted to illustrate some most important findings in this group. In this case the abolition of an associated amnesia did not relieve the patient's symptoms, nor did a moderate degree of excitement released by ether. It was when excitement under ether was stimulated to a climax and the phase of temporary transmarginal inhibition brought about that symptomatic recovery was produced.

Case 2.—E. C. C—, male, aged 47, was seen in a psychiatric out-patient department in December, 1944, when he complained that he had lost the use of his right hand since the previous June after a flying bomb incident.

There was nothing relevant in his family or early personal history. He had served in the 1914–18 war without breaking down, although gassed. In 1925 he attended hospital for a month because he had lost his sense of taste, and he has not recovered from this. Although a government clerk for many years, he was transferred from the permanent to the temporary staff in 1930 because of depression and inability to concentrate. His wife died a week before the bombing incident, but he had been separated from her for two years before this and his twin children were brought up by his mother-in-law. Patient was living alone. During the blitz in 1940–41 he showed no signs of nervous trouble, despite the fact that he had witnessed many distressing sights when working in a first-aid party attached to a local borough council.

He stated that he was quite fit before the flying bomb incident. His right hand was hit by some debris whilst he was helping to rescue some buried air-raid wardens, and he remembered no more till he found himself in his depot some ten minutes later. The total injury was a bruised right thumb and a sprain of the second metacarpo-phalangeal joint. A few days later his hand began to shake, and as there was no improvement it was put into plaster, and he attended hospital daily for 5 months for treatment with massage, hot and cold baths, and rug-making in the occupational therapy department. He continued to complain that he was unable to grip with his hand, which was cold and shaky, black and blue in cold weather. He was receiving a 25 per cent. disability pension.

Treatment under intravenous sodium amytal was twice carried out in outpatients and the short amnesia was clarified, but the shaking hand only stopped momentarily. On admission to hospital in February, 1945, the right hand showed a gross tremor, was cold, congested and bluish-red in colour. He could adduct and oppose fingers and thumb, but was unable to grip, and any voluntary movement caused an extreme increase in the tremor. He had a dilapidated run-down appearance, was mildly depressed and querulous, and complained also of a blurring of vision.

There was a moderate emotional display in the first abreaction under ether when he described some bombing experiences. As there was little improvement he was again abreacted under ether. This time he became violently excited, and the abreaction terminated in a phase of transmarginal inhibition. The hand stopped shaking and assumed a normal colour and temperature. The grip returned, and after some rehabilitation he was discharged.

We found that it was the chronic hysterical "stereotypies" of behaviour or thought that did best when excitement was stimulated to the point of transmarginal inhibition. Case 2 was motor stereotypy of six months' duration, while Case 3 is quoted to show that the same effect can be obtained in a stereotypy of thought of similar duration associated with features of depression and hysteria.

Case 3.—F. P—, female, aged 55, stated on admission: "I keep on going so funny and seeing different incidents with rockets that I have been through."

Family and personal history were normal, but she "has always been on the nervous side." There was no history of any previous breakdown. Her personality was described as very active and rather obsessional, with a tendency to

depression. She had been married 31 years, and her husband was a docker who drank heavily and was on strike at the time of her admission to hospital. They had no children. She had a hysterectomy in 1932. In 1939 she became a full-time air-raid warden, served in Dockland for 6 years and kept well despite numerous incidents. The symptoms began after her job as a warden became unnecessary with the ending of the war.

In March, 1945, she was involved in a rocket explosion, when her helmet was blown off and she felt something hit the back of her head. A lump came up, but she took no notice and helped in the rescue work. " I saw terrible sights ; plenty of people cut to pieces under the debris " (there were 50 casualties). A few months later she began to picture the incident, saw people cut and bleeding all over again, and could not get it out of her mind. If she closed her eyes she pictured the terrible sights, and had bad dreams. The symptoms were of 6 months' duration when she was admitted to hospital. At interview she was depressed and anxious, unable to concentrate, had lost considerable weight and complained of fainting attacks and giddiness. She had feelings of unreality, felt that people were talking about her, slept badly, and had almost completely lost the use of her legs. A neighbour stated that whereas she had been a very energetic and bright person, she was now forgetful and " flat."

Under light etherization patient relived the rocket incident with great emotional intensity and described how she was buried under the debris with her husband and brother. Her brother rescued her (he was decorated for his work), and then, during the abreaction, she frantically called and shouted for her husband : " Charlie ! Where are you, Charlie ? " she repeatedly shouted at the top of her voice, at the same time clawing with her fingers as though searching in the debris. The climax of the abreaction occurred when describing his rescue and she suddenly fell back and lay inert. This was a most dramatic result for, when the patient came round she had complete use of her limbs, said her mind was clear and that she had lost her fears. She remained active, well and cheerful, and regained her weight with the aid of modified insulin.

Another interesting finding was that it was not always essential, when doing an abreaction, to recall the precise incident or trauma that may have precipitated the breakdown. An artificial creation of stimuli of a more general kind may be sufficient. Thus one can use phantasy to create excitement, invent false situations or distortions of actual events when the uncovering of a true amnesia or the reliving of an actual experience has not brought about sufficient emotional release to disrupt a deeply ingrained neurotic pattern. Case 4 is quoted to illustrate this point. In this case it will be seen that when the reliving of the actual experience was insufficient, we deliberately distorted the actual experience under ether to produce the required degree of excitement in the subsequent abreaction.

Case 4.—A. H. H—, male, aged 29, complained, on admission to hospital in July, 1946, of insomnia, headaches, depression, attack of unconsciousness, loss of 1½ stones in weight and battle dreams, with nightmares about becoming blind.

He showed some neurotic traits in childhood. After a normal schooling he ran away to join the Navy in 1933 at the age of 17, but was invalided from the submarine service in 1938 following chlorine gas poisoning from leaking batteries. He was granted a gratuity. His domestic situation was complicated ; he divorced his wife in 1943, after five years of married life, because she had an illegitimate child (there is one child of his own), and he was unable to break away from his parents as he was an only son and his father was well-to-do. Although his general health was good he complained of abdominal pain and attacks of vomiting on and off since a cholecystectomy in 1942. He described himself as a good mixer, normally happy-go-lucky, fond of sports and reading, but very dependent on his parents and devoted to his mother.

Patient volunteered in September, 1939, rejoined the Navy and kept symptom-free until 1942, when he went down with the aircraft-carrier Hermes, but was rescued after some minutes' immersion. A few weeks later he had an attack of amoebic dysentery and was treated in hospital in Colombo for five months. During convalescence he developed acute abdominal pain, headaches and vomiting; the symptoms were relieved when his gall-bladder (said to have been perforated) was removed. As he had a recurrence a few weeks later of diarrhoea with blood and mucus he was invalided back to England in 1943. He soon volunteered for Naval Commandoes and took part in the landings in Sicily and Italy; his worst experiences were at Anzio. He remained free from illness during his 14 months in Italy, but in a rough sea *en route* to England vomiting began again and was followed by diarrhoea. Despite this he took part in the Normandy landings on D Day, but fell ill a week later with diarrhoea and was sent back. Frequent attacks ensued, and he was invalided from the Navy in December, 1945, with the diagnosis of "amoebic dysentery." He began work as a technical representative in his father's engineering firm, but three weeks later lost consciousness in the street, since when he had complained of frontal headaches. He again collapsed in April, 1946, and is said to have shown an icteric tinge of the conjunctivae. All physical investigations proved negative, and he was transferred to the psychiatric unit. At interview he was tense, sweating, restless and fidgety, and reproached himself for letting down his family and employers. He stated there were no gaps in his memory.

Patient was treated for several weeks by psychotherapy and modified insulin, and his weight increased by 10 lb. He expressed a desire to take up forestry work instead of returning to his father's employ, but as he continued to be tense and agitated with recurrent dreams of a flash and blindness, it was decided to carry out an ether abreaction. He said he was most affected by incidents in Italy, and by the fact that his ship went down off Walcheren and his mates were drowned whilst he was in hospital in Scotland, some months before the end of the war. At the abreaction, an incident, the bombing of Cape Passerole (1943), was chosen. He described how he was coxswain of a ship with an inexperienced crew and that he was the only one able to steer the vessel. At the time of the incident she was at dropped anchor. They were waiting for orders to go into action and patient was sun-bathing whilst he could hear bombers attacking the land. Suddenly a look-out man spotted an enemy plane, and when the order "action stations" was given he ran towards the bridge, but the ship was bombed. A bomb hit the bows, the captain and gunnery officer were killed and patient's leg was trapped under the collapsed chart table. He violently abreacted this episode, calling loudly for the sick-bay attendant during the abreaction, "Get me out. I can't use my leg." In the abreaction he kicked wildly with his right leg, but the left leg was immobile. In the actual incident he was released and able to steer the ship to safety. When the abreaction was over he continued details of the incident, for which he had previously a complete amnesia. He had no knowledge that his leg had been trapped and could now see the reason for complaints of a weak leg which he had frequently made after the incident. This trauma was not the precipitating incident of his neurosis.

A second abreaction was then carried out with the patient restrained in a jacket and during which he was even more violent. It ended in a "collapse" when he was told he was trapped and could not get away, so that he and his ship were doomed (in the actual incident he got away easily). Thus in the first abreaction an amnesia was uncovered with release of emotion and reproduction of details, but although he remembered all, he was no better. In the second abreaction an artificial situation was created, namely, that he was trapped and could not get away, with an artificial stimulation of anxiety terminating in a phase of total inhibition. On coming round he said, "The War has lifted. Something has lifted from my mind." Some days later he said he kept thinking about the events he had forgotten and other incidents, but he could now do so without worrying. He was soon fit for discharge.

Case 5 is quoted as a second example of this important finding. Here it was not till the patient was induced to abreact over being in a burning tank (in actual fact he was only near one) that a successful transmarginal inhibition was finally brought about with improvement.

CASE 5.—L. T—, male, aged 22, complained, on admission in May, 1946, of terrible depression, inability to concentrate, loss of confidence, and that all he could do was to sit around.

His father was an alcoholic and a man of violent tempers; his mother is a nervous worrying type. Patient was a rather nervous, timid, unsettled youth and apt to be bullied, but described himself as generally cheerful, fond of company, music and sport, sensitive, easily upset and prone to worry. He found it difficult to settle down at work, and did numerous jobs before his conscription in July, 1942.

He was quite well until his Normandy experiences. He landed on D plus 3, went into action the next day as a tank gunner and was not unduly nervous until he saw an Allied tank knocked out. From that time he was constantly waiting for a shell to come through and hit him, as he saw one tank after another destroyed and knew it would be his turn sooner or later. Even when he was withdrawn from action he would dive for cover if a shell landed as far as a hundred yards away. He ate little and hardly slept, but did not complain of his nerves. One particular incident worried him; when S.E. of Caen he jumped into his tank, as the shells were falling nearby, locked himself in and refused to come out. He was there for two hours waiting to be hit, was very scared, and did not want to see what was going on around him. When he did come out his mates just laughed it off. He did not think he could last much longer. The next day practically the whole of his regiment was lost in action. His tank was six miles inside the enemy's lines, but he did manage to get back. Soon after the tank was hit and set on fire, but he was outside it at the time. He found his way back to the allied lines and thought he was safe, but he was dive-bombed and wounded as he stood between some gliders. He hid under a disabled tank, and remembered the sound of the dive-bomber and the scream of the bomb. Something hit him in the face and arm, and he ran round in circles making a noise in an effort to get a bandage. He could not speak because his teeth were chattering; he was driven back to the R.A.P. and evacuated home. After four months' treatment in hospital for his wounds and a month's convalescence he returned to training duties, but found he could not swing across a river on a rope during a battle exercise. Then he realized he was not the same man, as such an exercise would not have given him any qualms prior to his Normandy experiences. A psychatrist sent him to a military neurosis centre, where he was re-graded C2 after several months' treatment, and he was transferred to general duties, but the symptoms persisted, and he had to rely on alcohol to help him carry on. On examination he was very tense, tearful, tremulous, agitated, restless, and preoccupied with memories of and dreams about Normandy, particularly the dive-bombing incident.

Under ether there was an extreme emotional display; short lived amnesias were revealed without relief. Finally he went into a state of transmarginal inhibition when he was deliberately induced to abreact his being trapped in a burning tank. There was an obvious relief of tension after this, and he said he felt free and relaxed. This improvement was maintained although he showed a slight jumpiness, so he was treated with modified insulin, regained his former weight, and left hospital well.

We also found, following this clue, that not only may distortion of real incidents be as effective as the abreaction of the incidents themselves in bringing about relief, but that successful abreaction can be carried out around non-specific incidents whose only use is that they can release a sufficient degree of excitement. Thus Case 6 shows that a patient may be relieved by using as an exciting stimulus an incident unconnected with the onset of the illness, and only occurring incidentally in its course. This is a case of depersonalization, the symptoms of which were finally resolved by an ether excitation when other treatments had failed, and the incident used to arouse the necessary excitement was the patient's experience of a mental hospital during the course of the illness.

CASE 6.—T. W—, male, aged 26, stated on admission to hospital in July, 1946, that he had remained in a daze since undergoing an operation for circumcision in India in the previous January.

He had been a rather nervous child, with fears of his father, who drank heavily and was quarrelsome at those times. He did quite well at school and, after four years as a shop assistant, joined the Army in 1940. His Army record was good and he was soon promoted to corporal (tradesman). Up to some months before the onset of his illness he was a cheerful, sociable person, with obsessional traits, but he became very worried when his fiancée wrote terminating their engagement. He was beginning to settle down and forget this before the operation.

A spinal anaesthetic was administered. Soon after, his head "went funny" and this feeling persisted. He said on admission, "Up to this very day I have not come out of that dazed condition. It seemed to dull my senses. I have not felt myself since. I am more or less in a different world. Everything seems unreal and I feel unreal. Things do not seem to be so distinct outside. I have no conception of time; it is not so precise as it was. Everything is automatic although I do my work. I can't grasp things." He also complained of headaches, pains at the back of his neck, loss of interest, inability to concentrate, and a feeling like a film over his right ear. When interviewed he was restless and tense, complained of palpitations, insomnia and fears of insanity. Prior to admission he had been sent to a mental hospital in error, but was discharged after a few days. Nevertheless this had increased his worry and unhappiness.

Patient had already been treated in India with E.C.T. and psychotherapy without success. A course of treatment with benzedrine, sedation and modified insulin was also ineffective. He was then abreacted under ether, but there was little emotional release until he was induced to relive his mental hospital experience, with emphasis on his fear that he would never get out again. This produced an emotional storm, and after the abreaction he said the tension had lifted. "I feel carefree." A few days later he became anxious again and lacked confidence. A second abreaction revolving entirely around the mental hospital incident produced further relief and he lost his symptoms of unreality.

Repeated abreactions under ether may be necessary in some cases. As many as four or five abreactions have often been given about the same remembered incidents before sufficient excitation has been achieved and for the patient to feel better. Repeated abreactions are often needed in reactively depressed patients, or those showing a general state of inhibition following an accumulation of stresses or blast. These patients may only require a simple re-excitation to break through inhibition, and do not always need the culminating transmarginal inhibition that proves helpful in the motor or sensory stereotypies as reported in Cases 1 and 2. Case 7 is quoted as a good example of those requiring two abreactions.

Case 7.—J. H—, male, aged 26, complained of headaches, inability to tolerate bangs, trains, etc., and pains in the lower back, which at times spread all over the body.

There was nothing relevant in his family history. He was "the ruffian of the family," and was nearly drowned when five years old. After two appearances in a juvenile court he settled down in adolescence and volunteered at the commencement of war. Before the onset of his illness he was a very happy person, fond of company and a good swimmer, and although he had a bad temper, it was under control.

Symptoms began in 1942, when a bad parachute jump resulted in a fall on his back and a dislocated shoulder. After some time he returned to the Parachute Regiment feeling fit, and went to Sicily in August, 1942. His plane was hit and he hurt his back as he baled out through the door, and he made a bad landing. Since then his "nerves began to go." In the Italian campaign he was dropped behind the German lines at Mount Etna, and found himself, with a broken knee and only able to crawl, alone between opposing barrages that went on for five days. He eventually reached the Eighth Army, and was sent in a highly nervous state to a Naval hospital.

After a period of remustering in Africa and further action in Italy, he returned to England in December, 1943. He had treatment for his back and was then

prepared for Arnhem, which he dreaded, but managed to conceal his fears. At the landing he fell across his wireless set and again hurt his back, but proceeded to Arnhem and experienced all the horrors of the fighting. He was the only survivor of his group of 17 and " then went mad." A house he was in was blown up and he had to run from house to house to escape German tanks and shells. He was accompanied by two other soldiers, but one was killed and the other wounded ; he carried the latter on his back. When he could no longer endure the conditions he remembers standing up, rushing across the road in front of a German column waving his hands and shouting, " Kill me, you bastards ! " Despite this he managed, under constant sniping, to dash across the Rhine, but was eventually captured. He was then subjected to ill-treatment for propaganda purposes and was compelled to crawl and be photographed. An S.S. officer blacked both his eyes, and the prisoners were marched many miles and jeered at *en route*. They then had six days without water in a cattle truck and reached " a louse-ridden camp." Here they lived on turnip-tops for 14 days ; he developed dysentery and was sent to another Stalag, where he had his first bath. Later he joined a working party in Berlin, but was sick with abscesses most of the time. He was working in coal mines when liberated by the Americans in April, 1945.

Patient was on a compassionate posting when admitted to hospital in March, 1946. He was tense, anxious, restless, irritable, sweating, and a stone under weight. He was suspicious, felt people were talking about him and was constantly ruminating over his experiences.

The first ether abreaction was only moderately successful, as he was unable to let himself go. He wanted to swear, but was subdued and inhibited and could not really place himself back to some of his terrible experiences. There was, however, some benefit, and he said, " I am on top of the world to-day," but he continued to complain of headaches and pains in his back. A week later he said, " I feel that if I could have a damn good scream I would be all right," and he remained tense and anxious. He put on 4 lb. in weight. In the second abreaction, incidents were clarified and there was far greater excitement with a better therapeutic result. After it he said, " I feel lighter in mind ; something has lifted." The next day he affirmed that something had definitely lifted from his mind and he felt better. A week later the improvement was maintained. " I feel a hundred per cent. better." He was soon fit for discharge.

In many patients excitement is stirred up by making use of suppressed aggression and fear. For instance, in Case 8 intravenous amytal showed that much aggression could be mobilized to create excitement. Going over the same ground with ether released this and produced the desired result.

Case 8.—S. W. E—, male, aged 26, complained, on admission to hospital in December, 1945, that he had become increasingly depressed for a year, was slow, unsociable, very concerned about his eyes and had headaches and suicidal thoughts.

His mother is highly strung, and a sister had been treated for depression in hospital. A maternal aunt is " hypochondriacal " and is in a mental hospital. In his early years he had no friends, as he was " kept behind bars " by his parents ; he was told that others in the house might upset his mother. After matriculating he studied business methods for two years, and had begun a business of his own before joining the R.A.F. in 1942.

He became a corporal-instructor in radio-mechanics and enjoyed 17 months in Iceland. When home on leave his house was bombed and he was buried under the debris. About that time he had been working long hours, as he felt " over-conscientious " during the flying bomb period, and he became very depressed. He was sent to Germany, where he finally broke down.

A course of sedation helped him to sleep better, but he remained depressed and retarded. Intravenous sodium amytal was then administered, and he talked with much affect over the unjust treatment meted out to the men by officers in Germany. He was on a welfare committee and tried to stand up for the men, but could do nothing. He accused the officers of " all sorts of things," was obviously much upset and displayed aggression and hatred. He failed to release much excitement.

As there was no change after this treatment, he was abreacted with ether on

the same topic. He was encouraged to shout, struggled violently when describing the attitude of the officers and released a good deal more aggression. There was intense relief after the abreaction and this was reinforced by psychotherapy. Three weeks later he complained only of a mild headache and occasional depression and returned to his unit.

There is no doubt that for uncovering an amnesia the use of an intravenous barbiturate, such as sodium amytal or sodium pentothal, is an excellent procedure. The same result may be attained by light etherization, but the barbiturate method is generally preferable as the excitement under ether often interferes with a full recital of events, and there is a tendency for an emotional climax to occur before the whole of the amnesia has been laid bare. Although it is frequently found that the patient, after an ether abreaction, goes on talking and completes the details of an amnesia, a prolonged amnesia is better dealt with under barbiturate administration. Nevertheless, one of the drawbacks of the barbiturate method is that if the patient is allowed to fall asleep after his treatment he may deny any knowledge of what has been uncovered whilst under the influence of the drug, i.e. the memories have not become integrated into consciousness. This disadvantage does not occur with etherization, as the patient does not usually fall asleep after the abreaction and is therefore able to retain and keep the memories in consciousness. Occasionally, however, we have failed to break through an amnesia under barbiturates, but succeeded with ether. In Case 9, after numerous attempts with intravenous barbiturates had failed, ether proved successful. Presumably in this case the inhibition and resistance could only be disrupted by the intense excitation produced under ether.

Case 9.—M. C—, male, aged 24, was first admitted to hospital in May, 1944, when he complained of slight headaches, dizzy attacks, forgetfulness, and a "browned off" feeling. His early history was uneventful, and he served for three years in the Irish Army before joining the British Army in 1942. There was a history of previous nervous breakdowns. Symptoms first began during the Italian campaign when he went to Tunis on leave and remembered nothing more till finding himself in hospital three weeks later. His papers stated that he had an acute hysterical breakdown following a period of severe stress in action. From this time he was constantly in trouble because he forgot things and could not tolerate anybody shouting at him. He was evacuated home, but as he pleaded to be retained in the Army his discharge was postponed and he was graded Category C, but failed to adjust. On admission to hospital he appeared anxious and depressed, but denied this and said he only objected to being shouted at or punished. He made little progress on routine treatment, and was invalided out of the Army in May, 1944.

Patient was readmitted in August, 1945, complaining of headaches, a fed-up feeling, and worry over his inability to recall events following the onset of his amnesia in Tunis. Several unsuccessful attempts had already been made to uncover the amnesia, including the use of intravenous barbiturates. He stated that he was involved in heavy fighting in which there was a large loss of life. Three of his mates on the machine gun he operated were killed on separate occasions. Soon after this he was given leave and went to Tunis. The last thing he could remember was coming out of a church and passing, on the church steps, a soldier offering shoe-laces for sale. Patient showed considerable distress when discussing this at interview, and burst into tears. He also said that after leaving hospital in 1944 he felt fed up for weeks at a time, was irritable and bad tempered as never before, and derived much relief from alcohol.

Intravenous sodium amytal was again tried on a few occasions in hospital, but failed to reveal details of the amnesia, although he displayed much aggression and some weeping when describing the fighting. A course of benzedrine and epanutin

failed to benefit him, and he became aggressive and unco-operative, refused to go to occupation classes and sat about reading. He expressed a constant anxiety about the recovery of his loss of memory, and appeared tearful, although he denied it, when remarks were made about his behaviour. An ether abreaction was then attempted, but he threw off the mask as he reached the events immediately leading up to the amnesia, and struggled so violently that the treatment had to be suspended because of insufficient staff to hold him down. A further attempt was made by administering intravenous sodium amytal followed by ether, but after a considerable abreaction over an incident unconnected with the amnesia, he again struggled too violently when the subject of the amnesia was approached. There was a subjective improvement, so it was decided to try another ether abreaction—this time with sufficient staff present to ensure any necessary restraint. There was a tremendous abreaction and the details of the amnesia were revealed. Briefly, he was accosted by an Italian who uttered some offensive remarks and patient "saw red," knocked the man down and trampled all over him until he lay motionless. Patient was stricken with the idea that he had killed the Italian, and in a panicky state he wandered about for a time, finally returning to his unit. His brother, who was also his commanding officer, covered his absence. Patient tried without success to obtain news concerning the man he had assaulted. When the ether abreaction was concluded he continued to fill in the details. It was considered that, in view of the nature of the material uncovered and which had been so strongly repressed he might not be able to cope with the knowledge, and he was therefore treated with a course of continuous narcosis for ten days. He was very restless and unco-operative, with aggressive outbursts, but the symptoms gradually abated and he was much improved when discharged from hospital.

Endogenous depressives can rarely be made to release emotion even under ether. Despite all attempts to stimulate excitement a dull recital of events is often the only result. But this is the sort of case which responds to the much greater degree of non-specific excitation obtained by electric shock therapy. Depressives responding to E.C.T. are generally stable personalities in a state of profound widespread inhibition. The disruptive stimulus of E.C.T. may prove too much for the less stable nervous system showing hysterical and reactive depressive features. The latter type of case can be re-excited with ether, whereas the endogenous depressive fails to respond. Ether in turn, as we shall show later, can be too disruptive for the chronic constitutional hysterical personality. Thus various types and degrees of excitation may be needed for the different types of nervous system. One is tempted to search for an explanation of the differences in action of E.C.T. and ether abreaction. Some differences, no doubt, are independent of the strength of stimulus, and one can but speculate, for instance, on whether the action of ether abreaction is more cortical, whereas E.C.T. acts more powerfully on the whole brain and particularly the autonomic nervous system. The latter suggestion is the belief of Gellhorn (31) based on his experimental work on rats. Whatever the explanation, it is significant that abreaction, E.C.T. and insulin, are treatments which, at different levels of nervous activity, produce their best results by an initial excitation carried to the point of temporary cortical inhibition. A subshock E.C.T. may be as ineffective as an incomplete insulin coma or an ether abreaction which does not reach the stage of collapse.* These comparisons need further investigation and study before any conclusions can be drawn, but two cases are worth quoting. In Case 10 E.C.T. succeeded where abreaction failed in

* In our experience the best results from E.C.T. treatment generally occur in those showing the profoundest relaxation after the fits. Likewise, E.C.T. given under insulin sopor may sometimes produce better results than E.C.T. alone, perhaps due to the greater final relaxation obtained in this manner.

an endogenous depressive, whereas Case 11 illustrates a successful result with abreaction in a patient suffering from reactive depression after E.C.T. had produced no change.

Case 10.—W. D—, male, aged 48, a police inspector, was first seen in out-patients in January, 1946, when he complained of depression.

There was nothing relevant in his family or personal history, and he had a good record. His previous personality was that of a rather rigid obsessional with a hasty temper at times, but fond of company and fairly happy.

His symptoms began in 1940 after he was buried in his home when it received a direct hit from a bomb. He was trapped for some hours with his head " doubled under him " and he felt himself slowly choking. In addition he sustained injuries to his right shoulder and ribs and concussion ; despite three months in hospital he felt " a bag of nerves," was sleepless, tense, giddy, tremulous and tearful. A course of analytical treatment failed and he returned to work in a tense state and lacking confidence. His work entailed supervising bomb incidents. " I felt like crawling under the ground. Knowing other people were trapped in these incidents had a hellish effect. I lived it all over again." Although he carried on he became increasingly depressed. On examination he was depressed, anxious, tired, and found it an effort to concentrate or maintain interest. He felt people were looking at him and that he was misunderstood, and became impatient and resentful. There was a recent marked increase in weight, and it was thought that the depression was either complicated by myxoedema or of a menopausal type.

An ether abreaction produced little emotion and there was a rather dull recital. He did, however, become flushed and a little excited when describing the bomb incident. There was some improvement, and ether was tried a second time, but produced no real break through his depressed state. It was therefore decided to try the effect of E.C.T., as testosterone, thyroid and benzedrine had also failed to effect an improvement. He was able to return to work in a fit condition after four E.C.Ts.

Case 11.—H. L—, male, aged 44, gave a history, when first seen in out-patients in August, 1945, of a feeling that there was something over his face all the time, and that he was unable to feel over it.

There was nothing of note in his family or personal history. He was a professional boxer of some standing and had never been knocked out. His previous personality was that of an obsessional though cheerful individual.

The duration of symptoms was six years without fluctuation, and he became increasingly worried and depressed. The onset was sudden, whilst he was working in a conservatory. " I will never forget it. I was planning a fire curb when I suddenly felt as though something hit me in front of the head. After that everything seemed different. I am there and yet I am not there. I feel there is no world around me. There is a strip in front of the face and all feels black before me. It feels like a lump in the forehead, and I have an empty feeling in the pit of the stomach as though the breathing centre is not there." Before the onset of symptoms he was unable to rid himself of an attack of pediculi pubis. This worried him greatly, as he was scrupulously particular about personal cleanliness. The condition was eventually cured by his doctor and the depersonalization followed. On admission to hospital he was depressed, anxious, unable to concentrate, had bad dreams, and was preoccupied with ideas of suicide. Five E.C.Ts. produced little change. He was then abreacted under ether. There was an extreme emotional outburst over the " crabs " incident, but the symptoms remained unaltered. He was immediately abreacted again, this time to the stage of transmarginal inhibition. On coming round he stated " There was something round my head which has now gone. My head is relieved. I have lost the feelings of unreality. I feel different altogether." This was maintained, and he was discharged from hospital free of symptoms.

We have learned as much about the mechanics of abreaction from our many failures as from our successes. For instance, we have tried the effect of ether abreaction in a small number of cases of chronic obsessional neurosis. We

wished to find out if we could produce in such cases a state of excitation followed by transmarginal inhibition and whether it might be possible to disrupt the pattern of rumination around a particular idea or fear. We did not succeed. It is difficult to excite or abreact such patients, as they are too precise, rigid and meticulous to picture with emotion an incident not happening at that particular moment. They tend to answer "Yes, doctor," or "No, doctor," when attempts are made to induce them to re-enact certain events. If, however, they do become excited they may be made temporarily worse by the abreaction. This result is not surprising in the light of Pavlov's concepts. In such case there is often already an abnormal predominance of the excitatory process, an abnormal "inertness" or "pathological inertness" in points or areas of the cortex. We have found that when there is a useful response to abreaction there are generally hysterical or reactive depressive components to the total picture, or an accompanying state of depersonalization—all these suggest the presence of inhibitory phenomena which excitation under ether may loosen. In Case 6 we have already described a case of depersonalization with obsessional rumination relieved by abreaction, and in Case 12 an obsessional phobia occurring in a setting of depression was disrupted by one E.C.T. followed by a particularly severe ether abreaction which produced a transient state of dissociation yet lead to recovery.

Case 12.—T. H. A. M—, male, aged 32, said, on admission in December, 1945, "I am convinced I have syphilis. I was depressed, but accept it now."

Patient's mother was nervous, and one of his sisters was in a mental hospital. He had been a sensitive, timid youth, did well at school, gained a University Scholarship and had a First Class Honours degree in Engineering. He had no sexual experience, and though engaged at one time, he terminated it because of his ideas. His previous personality was described as anxious, shy, solitary, and a ruminative obsessional.

He first thought he had syphilis when, in adolescence, his penis was tender after ejaculation, and he kept this knowledge to himself. Two years later he suffered from dysuria and a retracted testicle. This increased his fears about syphilis, but he carried on "normally" until 1941, when he had a feeling of falling to one side. His memory began to fail, and in June, 1945, his libido diminished and his skin became anaesthetic in parts. His brain felt "clogged with thoughts like treacle," and he lost interest. Before June he was "keyed-up" by strong sexual feelings, but since then everything was flat. He experienced a clear discharge after an erection and this meant syphilis. Throughout the illness he carried on as a Post Office engineer and first consulted a doctor four months before admission. Several Wassermann reactions, done privately and in hospital, were negative, but this, and the fact that his C.S.F. was negative, made no difference to his symptoms. On admission he was very dull and apathetic, sat in a chair most of the day, and believed that his syphilis was either due to the fact that his father was a bailiff in a mental hospital, or that he had contracted it from the lavatory seats in Portsmouth dockyards. He blamed himself for not mentioning it when he first contracted it, and showed practically no insight. There were also some hypochondriacal symptoms, which he attributed to syphilis, such as the dead feeling of his skin, and he said he was emotionally dead, had ceased to worry and was sleeping badly.

This man was suffering from an obsessional neurosis with severe depression, and it was decided to try E.C.T. Unfortunately he sustained a vertebral crush fracture at the first treatment and refused any more. Nevertheless, he said that on the day of the treatment and the next he felt alive again, but this wore off. He was then abreacted under ether, using, as stimuli, his fears of syphilis and his bombing experiences. He abreacted for a time with considerable force, and then appeared to go into a dissociated state. This lasted a few hours and there were marked fluctuations in awareness. He insisted on staring out of the window, talked

random nonsense, and would then appear normal for a while. Although he said he was improved, it was difficult to assess the extent. There was no doubt about this later on, as he was much happier, active, mixed for the first time with patients in the ward and attended the occupational departments. The following week he was " more alive although the skin was partially dead," but he said that he hardly gave a thought to syphilis, despite his absence of libido. A fortnight later he was no longer depressed, called his old ideas " rubbish " and returned to work.

If severe chronic hysterics are treated by excitatory abreaction they rapidly become inhibited or dissociated when any strong stimulus is applied. As soon as they show an emotional release, or attempt to relieve incidents that have produced distress in the past or artificial situations of some emotional significance are created, they inhibit or dissociate. As with Pavlov's weaker dogs, they show chaotic cortical function or total inhibition again and again following slight excitation, and their past record shows little stability in response either to upbringing or environment. Never having had a stable balance, continual re-excitation only makes them more unstable. Thus severe chronic hysterics do not as a rule benefit from ether abreaction. If at all, they are helped more by gradual release of tension under barbiturate. Benefit from ether is confined to the previously stable person who has developed hysterical symptoms following severe stress.

In mixed cases, showing for example stammers, amnesias, tremors and anxiety, the combined use of barbiturates and ether has often been necessary to produce a good result, either alone being insufficient. At various stages of therapy it may be necessary to damp down or re-excite in treatment. Case 13 is also a good example of the combined method, each type of abreaction being used at different stages of treatment. Barbiturates at first were used to get rough details of the traumatic incident. Then ether was used to produce a high degree of excitement and restore the use of a limb paralysed for one year. Finally, barbiturates were again employed to complete a more exploratory type of abreaction, and round off the recovery with additional psychotherapy and reassurance.

Case 13.—W. F—, male, aged 35, complained of " black-outs " of three years' duration and which were becoming more frequent. He also complained of depression, insomnia and nightmares, and made a mention of his paralysed left arm.

There was nothing of note in his family history. His early home life was difficult because of the frequent absence of his father, and financial difficulties. He was a good scholar and, although shy, enjoyed games and took a great interest in physical training. He became an instructor at a boys' club, and did some short-term jobs before joining the Army in 1940. He volunteered as a Commando, took part in the Dieppe and other Commando raids, and was wounded through the left shoulder in June, 1944. When admitted to our unit a year later he still had shrapnel behind the scapula and in the pectoral muscles. Physical examination showed multiple scars round the upper left arm and scapular regions where operations for the removal of shrapnel had been carried out. There was wasting of muscles, and the left hand was cold and apparently useless. Patient said he was " desperately worried about being unable to use his arm," although he also said, " I realize it is a psychological paralysis."

Under intravenous sodium amytal he became upset when describing a number of incidents as a Commando, including the shooting of a child and the loss of a friend after he had promised this man's wife that he would look after him. Patient felt much improved after this treatment, and said he was " lighter " and better than he had been for months. He used his left hand a little, but free movement was very limited, although he " felt sure it would come." There was a reluctance

to discuss his experiences, about which he showed evident guilt feelings. An ether abreaction was therefore carried out, and he reacted very strongly to the death of his friend and the shooting of the child. He explained that he had to kill this child in a Commando raid to prevent her giving the alarm. After the abreaction there was almost full range in movement of the left shoulder for the first time, and he was able to engage in a sparring match with one of the doctors. A week later, though cheerful, the movement of his arm was somewhat limited. At times he felt " very scared and tense inside " and had four " black-outs," but they did not last so long as before, and there were now no violent outbursts during the attacks. A further intravenous sodium amytal injection was carried out, to which he reacted immediately and violently, and relived several commando raid experiences. He returned to the incident of the child, and for the first time disclosed that he had strangled her with his left hand. He felt intense guilt, but knew he had to commit the act to save his men. As a father he could not forgive himself, nor could he bear to see children suffer. There was also some discussion about a very unhappy childhood and his upbringing by a strict grandmother. He had seen so much suffering by children on Tyneside that he could not tolerate thinking about it. Suggestion and reassurance under amytal relieved considerable guilt feelings, he appeared able to forgive himself and used his arm quite freely. From this time he was completely at ease and talked without excessive emotion.

Finally a note of caution is necessary. We have stressed the many failures in treatment by abreaction. A serious aspect is that in inexperienced hands ether abreaction may precipitate a temporary psychotic episode requiring the patient's removal to an observation ward. This has happened on only one occasion in our series of several hundred abreactions despite the uncovering of many severe traumatic incidents. Hence the importance of suitable selection of cases, necessitating first a careful assessment of the patient, his past history, personality and the psychopathology of his illness, together with skill in controlling disturbing symptoms by other methods of treatment.

Discussion.

Throughout the war, especially during the times that our hospital unit of neurotic soldiers was subjected to intermittent bombing, we were impressed with the fact that many barbiturate " narcoanalysis " recoveries were in part physiologically determined. The brain was being influenced by a drug in a way that made it readily give up its patterns of hysterical behaviour, especially before they had become deeply ingrained (30).

We gained this impression even more forcibly with our experiences of ether abreaction. Therefore we have searched back through other disciplines for instances of similar happenings, each given by their exponents a different metaphysical explanation. It seems to us that the phenomena we observed in their extreme form in ether abreaction are very similar to phenomena seen throughout the ages, when the brain of an individual has been subjected to emotional excitation, often leading to a phase of temporary cortical inhibition with " rupture" of pre-existing patterns of thought and behaviour. There seems to us to be a basic physiological pattern running through procedures as far apart as the rites of the Corybantes and the catharsis of Freudian psychoanalysis. Within its scope are religious conversions, orgiastic rituals, tribal dancing, the use of mescaline in primitive religious ceremonies, and other methods of producing rising emotional excitement, leading to exhaustion followed by changes in mental outlook.

In primitive medicine sufferers from mental disease were thought to be possessed by a spirit or demon, and were treated by purifications and incantations. Aristotle, in his account of Greek tragedy, is quoted as saying, "Tragedy is a representation . . . which by means of pity and fear effects the purgation of such emotions." Thomson (32), in *Aeschylus and Athens*, discussing this says Aristotle implies that before the morbid affections can be expelled, they must be first artificially stimulated. In primitive Greek magico-medical secret societies, such as those of the Corybantes, "madness" was induced and cured by a ritual of incantations and an orgiastic dance to the accompaniment of flutes and drums. The spirit was first roused into activity and then expelled. It is interesting that the exorcists were selected from those initiates who had experienced the privilege of exorcism. Aristotle, in this connection, said, "The initiates were not required to learn anything, but to experience certain emotions and to be put in a certain disposition." This certain disposition was the artificial excitation of fear, whereby the emotions were then released.

Celsus, the recorder of medical thought in Roman times, in common with the majority of Greek and Roman physicians, recommended dungeons, fetters, purgation and starvation of the mentally deranged. He claimed by these means that certain memories were refreshed, and said, "It is also beneficial to make use of sudden fright, for a change may be effected by withdrawing the mind from that state in which it has been" (Zilboorg, 33). Magic and superstition reigned throughout the Dark Ages; the mentally sick were in the hands of the priest, and treatment was based on ideas of treatment of the devil. Here again excitation was a prominent feature. Nolan Lewis (34) describes three main groups of curious mental reactions in Central Europe in the Middle Ages: "(1) Epidemics of flagellants who gathered into large processions and travelled over the country bearing crosses, banners and candles, doing public penance for their sins; they marched, prayed, sang and shouted and flogged the upper parts of their bodies until blood came. . . . (2) The 'dance mania' characterized by an urge of dance, laugh, sing and make other noises until completely exhausted. . . . (3) Devil possession; the devil was supposed to choke, push, pull and throw its victim about, causing him to become excited, violent and froth at the mouth. It was then up to someone with spiritual power to exorcise the demon. During this procedure, if successful, the devil jumped out with a sudden jerk."

Symptoms of neurosis were regarded as manifestations of the influence of Satan, and almost all mentally sick were accused of being witches or sorcerers. This continued to the eighteenth century, and the theologians alone could fight the menace. Bromberg (35), in *The Mind of Man*, gives an account of a notable exorcist, St. Norbert, who attempted to exorcise a possessed woman. Resemblance to modern excitatory abreaction is obvious. He made repeated attempts in the presence of the people but "the devil mocked him." Further attempts with the girl immersed in water and her hair cut off also failed. The Saint thereupon fasted and prayed. "On the following morning he prepared to say Mass; the girl was again brought, and the people gathered to witness the combat between the priest and the demon. Norbert ordered two men to hold

the possessed not far from the altar . . . and several passages were read over her head. The demon still mocked, and when the priest next elevated the Host, it cried out: 'See how he holds his little god between his hands!' This made the priest of the Lord tremble, and gathering up all his strength, he began to attack the demon in his prayers and to torment him. Then the demon cried out through the mouth of the girl: 'I burn! I burn!' Then the voice howled: 'I die! I die!' Then a third time: 'I want to go! I want to go! Send me away!' Two men held the possessed woman strongly. But the demon did not let himself be stopped. He escaped, abandoning the vessel he had possessed, and leaving behind him nauseating smells. The girl fell to the ground. She was taken back to her father's house, took nourishment and soon completely returned to health."

In the eighteenth century, although chains and fetters were beginning to be abolished, even Christian Johann Reil recommended "non-injurious torture." He considered it legitimate to throw patients into water, and fire cannons to bring patients to their senses, and believed it was useful to arouse anger, disgust and pain in certain cases.

The short history of a variety of conditions already mentioned suggests that the phenomenon of massive excitation, especially when carried to the point of collapse, is possibly one of the underlying mechanisms of relief. Many other examples can be quoted.

Franz Anton Mesmer's remarkable results, for instance, are generally attributed to suggestion, but, although doubtless this played a part, we suggest that the excitation produced was one of the important factors in the production of results. Mesmer used the baquet, a large wooden tub filled with bottles in and around which was "magnetized" water. Patients sat round this holding rods protruding from the baquet and they were touched by a "magnetized" wand held by Mesmer wearing a lilac silk coat. "Soon signs of restlessness appeared, the patients would twitch and tremble violently, while convulsive movements of the hands and body muscles increased in tempo, until palpitating and convulsed they achieved the 'grand crisis', ('crisis of exaltation'). Without a crisis there could be no cure" (35). Mass convulsions were produced under mesmerism. An eye witness described it thus: "Some patients remain calm, and experience nothing; others cough, spit, feel slight pain, a local or general heat, and fall into sweats; others are agitated and tormented . . . by involuntary jerking movements in all the limbs, and in the whole body, by contraction of the throat, by twitchings in the hypochondriac and epigastric regions, by dimness and rolling of the eyes, by piercing cries, tears, hiccough and immoderate laughter. . . . They are all so submissive to the magnetizer that even when they appear to be in a stupor, his voice, a glance or sign will rouse them from it. . . . When the agitation exceeds certain limits the patients are transported into a padded room; the women's corsets are unlaced, and they may then strike their heads against the padded walls without doing themselves any injury." A lengthy report by the Academy of Science vividly describes the state of excitation induced, and continues: "This last stage, which terminates the sweetest emotion, is often a convulsion. . . . To this condition there succeed languor, prostration, and

a sort of slumber of the senses, which is a repose necessary after strong agitation" (35).

Similar techniques have played a prominent part in movements concerned with religious conversion or salvation. It was, and still is at the present time, common for abreaction to occur to groups or individuals at revivalist meetings. In 1820, Charles G. Finney, an American evangelist and self-styled "Brigadier-General of Jesus Christ," had grasped the fundamental principles of excitatory abreaction, when he would exhort his audience with violent gestures to "Agonize, I tell you; why don't you agonize?" Searching through the literature we find many reports of acute excitement followed by collapse resulting in profound alterations of thought and behaviour, particularly in accounts of sudden religious conversions of various kinds. James' *Varieties of Religious Experience* (36) contains records of this. John Wesley, in the eighteenth century, insisted that effective conversion is usually accompanied by a profound emotional experience, and his diary contains a mass of factual data. Using a fear-provoking technique in preaching, he records detailed descriptions of individuals or groups showing increasing excitement and collapse leading to instantaneous and unexpected conversions (37).

Thomas Butts (38), writing in 1743 about these conversions, says: "As to persons crying out or being in fits, I shall not pretend to account exactly for that, but only make this observation: It is well known that most of them who have been so exercised were before of no religion at all, but they have since received a sense of pardon, have peace and joy in believing, and are now more holy and happy than ever they were before. And if this be so, no matter what remarks are made on their fits."

John Wesley suspected a physiological component to the phenomena that occurred with his preaching. He is quoted as saying: "They can be accounted for on principles of reason. How easy is it to suppose that a strong, lively and sudden apprehension of the hideousness of sin and wrath of God and the bitter pains of eternal death should affect the body as well as the soul, suspending the laws of vital union, and interrupting or disturbing the ordinary circulation and putting nature out of its course" (39). And he also found by experience the necessity of stabilizing the change to prevent relapse. While insisting that the initial change should generally be an instantaneous process, he then divided the converts into small groups under a leader to meet once a week. His rules for the conduct of these groups can be profitably studied to-day by those interested in the group treatment of neuroses (40). Historians now recognize that by this combined technique he was able to change the face of England at a critical era.

Arriving at the present century we find, in psychoanalysis, where there occurs a slow and prolonged mild abreaction, critical periods arise in which there is a much more powerful abreaction. This may sometimes terminate in a phase of temporary collapse and sudden progress in treatment.

Modern psychotherapy and religion bear out Pavlov's observation that once an animal or human being is "changed" by such a process, new patterns of

behaviour or new ideas may often be implanted on the altered soil. Further individual or group psychotherapy is generally necessary to achieve this. New aims may be given once the patient is released from his old neurotic adjustments. Patients must be reconditioned. They are often left in a temporarily suggestible state, particularly if the abreaction has culminated in an ultra-paradoxical phase. A transference situation is established, corresponding to that of the positive transference created by the analysts. They are thus open to new ideas, and in a position to accept what is held out to them. However, like Pavlov's dogs, weaker individuals relapse and may even become worse, but the better type of personality remains steadfast in a subsequent adjustment.

Attempts in the past to account for the beneficial effects of emotional release in psychopathological or metaphysical terms alone seem inadequate to us. McDougall (41) insists that the essential therapeutic step is the relief of a dissociation such as an amnesia, and assigns a very subordinate role to the emotional excitement. Kardiner (5) considers that in the traumatic neurosis there is a disorganization or contraction of the ego, the primary symptom being inhibitory and later symptoms adaptive attempts. In the acute cases (before the ego structure has been altered) abreaction assists in bringing about a re-integration, but, says Kardiner, "the therapeutic measures used successfully in treating these neuroses had very little to do with the conception of the psychopathology." Grinker and Spiegel (42) believe that a progressive weakening of the ego occurs in its relationship with the sources of anxiety, ending finally in a complete elimination of normal ego mechanisms. In some cases the anxiety is concentrated and the remainder of the ego is allowed to function in a stable and efficient manner. Abreaction allows a freeing of the ego. Some consider that in the course of an emotional abreaction the patient is placed in a hypnotic or "hypnoidal" state, and that the abreaction which takes place and its beneficial results are due to suggestion. Our findings suggest that simple physiological mechanisms may play a larger part than has hitherto been stressed.

Summary.

1. The literature on abreaction, and the Pavlovian physiology with a possible bearing on the mechanisms involved, are reviewed.

2. The use of ether in facilitating excitatory types of abreaction and comparisons with the barbiturates are discussed.

3. Experimental observations arising out of the use of excitatory abreaction for the relief of various types of neurotic illness are reported. Indications and contra-indications to the employment of this treatment are given. Relevant case histories are quoted.

4. The findings in modern drug abreaction are compared to other similar findings reported in the various forms of religious and psychological healing throughout the ages.

We wish to thank Dr. Louis Minski for providing us with the facilities and the extensive case material available at Sutton which enabled such a research to be undertaken.

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THE EXISTENCE OF CRITICAL LEVELS FOR THE ACTIONS OF HORMONES AND ENZYMES, WITH SOME THERAPEUTIC APPLICATIONS.*

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Does convulsive therapy in the depressive states produce its effect by some action on the pituitary and hypothalamus? This is a question which we at Barnwood House and at the Burden Neurological Institute are trying to answer.

That this working hypothesis is not unreasonable is suggested by a variety of facts, to some of which I may make a brief reference. There is, for instance, the well-marked tendency for depressive states to occur at the menopause, that is, when there are qualitative changes in the gonadotropic hormones secreted by the pituitary. There is the resemblance between the retardation and apathy of the depressive states and the loss of spontaneous activity shown so markedly by the rat after hypophysectomy. There is the observation of Hemphill, Macleod and Reiss (1942) that after convulsive therapy there is an increased excretion of ketosteroids, the latter's production being probably dependent on the corticotropic hormone of the pituitary. There is the transient improvement sometimes seen after the exhibition of sodium amytal, whose main effect falls probably on the diencephalon. There is the profound affective disorder of the depressive state, suggesting disorder at a thalamic or lower level. There is Masserman's work (1939) which shows that the hypothalamic centres are highly sensitive to cardiazol, and there is the observation that subconvulsive doses of cardiazol lead to an intense affective disturbance, suggesting action at a thalamic or lower level. Finally, it is possible that the depressive states and the effect of convulsive therapy are expressions of metabolic change: no regions of the body are richer in centres of metabolic control than the pituitary and hypothalamus.

Be this as it may, the relation of pituitary function to convulsive therapy is being studied here by a variety of methods. In this paper, however, I shall be concerned with only one small aspect of these investigations.

The pituitary works, of course, by the action of its hormones. Pituitary action is hormone action. Now there is a growing conviction among biochemists that hormones, as well as vitamins and many drugs, produce their effects primarily by influencing specific enyzmes. Enzymes are being dis-

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covered in greater and greater numbers, and almost every metabolic step seems to be controlled by a specific enzyme. Thus the burning of glucose to carbon dioxide and water is now known to involve many dozens of enzymes, each playing a small but essential part in the intricate processes of this change. Further, whatever controls these enzymes controls the processes.

The possibility that these enzymes might be controlled or affected by hormones was suggested long ago, but this remained an idle speculation in the absence of actual examples. The last decade, however, has been one of rapid advances, and actual examples are now being discovered with increasing frequency. Of the vitamins, four are now known to be essential component parts of certain enzymes, so that lack of the vitamin causes lack of the corresponding enzyme. Of drugs, at least fourteen are now known to produce their characteristic effects by inhibiting a particular enzyme. The hormones have been slower in revealing their relationships to the enzymes, but a start has been made by Cori's discovery (1945) that a hormone from the anterior pituitary inhibits the enzyme hexokinase—an enzyme essential in carbohydrate metabolism. It seems probable, therefore, that the other hormones will also be found to produce their effects by acting on particular enzymes. Green (1946) summarizes the modern outlook by saying, "All dynamic activities of the cell must be reducible to terms of enzyme chemistry. Physiological function and enzyme chemistry are two sides of the same coin." *The concept of metabolic change or disorder therefore implies change or disorder in the body's systems of enzymes.*

Now it is well known that an enzyme controls a chemical process by altering only the velocity with which the process occurs. Lack of an enzyme, or a hormone, can therefore produce directly a change in velocity only, and if it is suggested that some psychiatric disorders are associated with metabolic changes, it may be objected that a simple change of velocity is quite inadequate to explain the great changes of behaviour seen in the psychoses. Is it possible that a mere decrease of some hormone or enzyme could produce in behaviour a change gross and catastrophic? Would not the lack of some enzyme lead merely to a general slowing down of the brain's activity, so that the person's behaviour would be merely slower while still remaining essentially normal in type? Is not this, in fact, what is observed to happen in the milder degrees of hypothyroidism?

The aim of this paper is to show that this line of argument is unreliable. *I shall show that if the amount of some hormone or enzyme is gradually reduced, there is no limit to the suddenness with which an effect may appear nor to the intensity of catastrophic change which may occur.* This paper is intended to demonstrate this fact and to indicate its consequences.

* * * * *

The first point to be noted is that, though controlled by enzymes, the metabolic systems are dynamic by their own activity. The amount of enzyme present acts like a tap, controlling the rate at which the atoms proceed from one molecular arrangement to another, but once the atoms are past the control their behaviour depends only on their own activity. We see a similar state

in the Bunsen burner where the tap, corresponding to the enzyme, regulates the flow of gas, but the subsequent combustion of the gas depends on its own chemical nature and owes nothing to the tap.

A system containing enzyme, substrates and products, being dynamic, is subject to the general principles of dynamic systems (Ashby, 1946, 1947). One of these principles is that, in a dynamic system of any type whatever, a change of velocity, far from being trivial, may have the most widespread effects and may lead to behaviour of very different type. A simple illustration is given by the Bunsen burner when it "strikes back." What happens is as follows: In a burning mixture of gas and air, the flame is propagated with a velocity depending on the proportions of gas and air. The edge of the flame is shown visually by the blue cone. The position of the cone depends on the opposition of two dynamic factors: on the one hand the mixture of gas and air travels up the tube with a movement which tends to blow the flame away from the top of the tube, while on the other hand the flame burns downwards into the rising mixture. Ordinarily the two are in a dynamic equilibrium, the two velocities are equal and opposite, and the position of the cone is steady. If now we alter the flow of the mixture through the tube by slowly turning the tap, altering only the velocity, we find that little happens until the velocity falls below a critical value. When the velocity falls below it the system becomes unstable and passes over catastrophically to a different way of burning.

It will be seen, therefore, that in a dynamic system a change of velocity is in no way restricted to producing only a proportional slowing of the other events in the system. On the contrary, a slowing down may render a stable system unstable, and may result in a change both sudden and catastrophic. I do not, of course, suggest that this sensitivity to velocity is shown by *all* chemical reactions. But where it does occur it is usually important. Here I am concerned only to demonstrate its existence.

Having given this example in the Bunsen burner in order to show the generality of the principles involved, I will now turn to an example in chemical dynamics. The system I shall describe shows some interesting features not, so far as I am aware, previously described. The system has been discovered primarily because the basic dynamic theory has been established (e.g. Ashby, 1946, 1947), and it is easy to find something when one knows what one is looking for. I select an example as simple as possible.

We start with two reactions progressing autocatalytically:

$$A \rightarrow B$$
$$A \rightarrow C$$

a substance A turning monomolecularly into two others, B and C. To keep the reaction going, we assume that there is a steady addition of A to the system from some outside source, as a substance might be supplied to a tissue from the blood stream passing by. To prevent B and C from accumulating excessively we suppose they are removed from the system at rates proportional to their concentrations, as would happen if they diffused away into the blood stream. (These last two assumptions are not important, and could be varied without affecting the argument). We now assume that the reaction "$A \rightarrow C$"

is catalyzed by an enzyme, and therefore is partially controlled by it. (This is really quite a simple type of system, and the assumptions involve nothing unusual. It is certainly simple when compared with, say, the oxidation of glucose with its many dozens of enzymes acting in complicated chains and cycles.)

I may now proceed to demonstrate the behaviour of this system. Its "behaviour" is defined as the variations in time of the amounts of substances A, B and C. Owing to the chemical transformations which occur, these amounts will change with time: we shall follow these changes, noting particularly how they are affected by the enzyme.

In the simplest case, the system will behave according to the equations

$$\left.\begin{aligned} \frac{dx}{dt} &= a - kxy - lxz \\ \frac{dy}{dt} &= kxy - my \\ \frac{dz}{dt} &= lxz - nz \end{aligned}\right\}$$

where x, y and z are the concentrations of A, B and C respectively; a is the rate of addition of A; k and l are the velocity constants of the two reactions; and m and n are the coefficients of proportionality of the diffusions of B and C. The equations are non-linear and therefore cannot be solved explicitly, but they are easily solved numerically by the Adams-Bashforth process; this has been done here.

The results show that this chemical system, however started, soon settles to an equilibrium, after which all three constituents remain at constant concentrations. (Although the concentrations remain steady, yet there is a continuous flow of actual substance occurring—just as the cone of a Bunsen burner is steady in position, although a flow of gas molecules through it is occurring continually. Substance A, for instance, is continuously augmented by the steady inflow, but is continuously diminished by the transformation to B and C. When the gain and the loss are equal, then the amount of A remains steady.) The first characteristic of this system, then, is that it settles down to a steady state.

We now ask how this steady state depends on the amount of enzyme present, and we shall find the effect to be striking and peculiar.

Suppose we set up a series of experiments keeping all conditions constant, but starting each experiment with a different amount of enzyme. Considering only substance C for simplicity and graphing the results in a typical case we get the curves of Fig. 1. The ordinate measures the amount of C present, while time progresses from left to right. Six different curves are given on the same diagram, each showing what happens to the concentration of C with each amount of enzyme. E gives the amount of enzyme in arbitrary units for each curve. Thus, with 2 units of enzyme present the quantity of C increases to a maximal value and then remains steady. The essential point is that whatever amount of enzyme is present, the number of possible end-

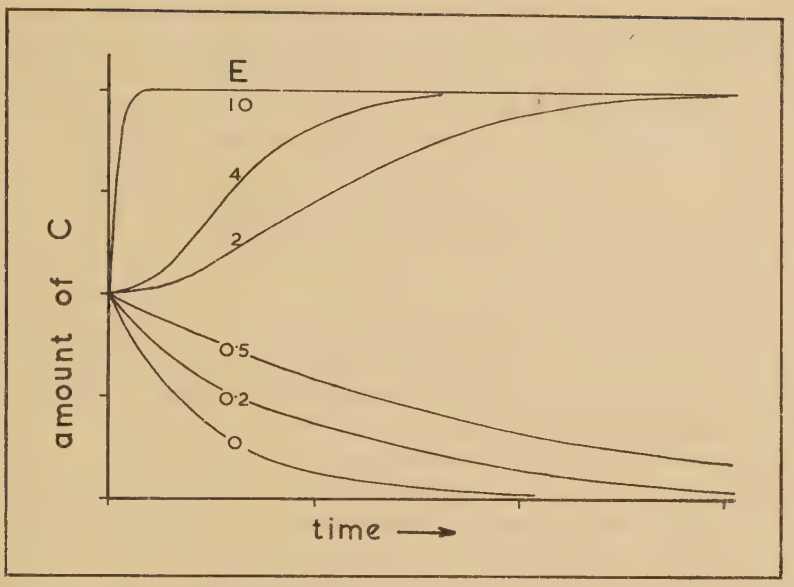

FIG. 1.—Varying amounts of E (shown in the column of numbers) results eventually in C changing to one of only two values.

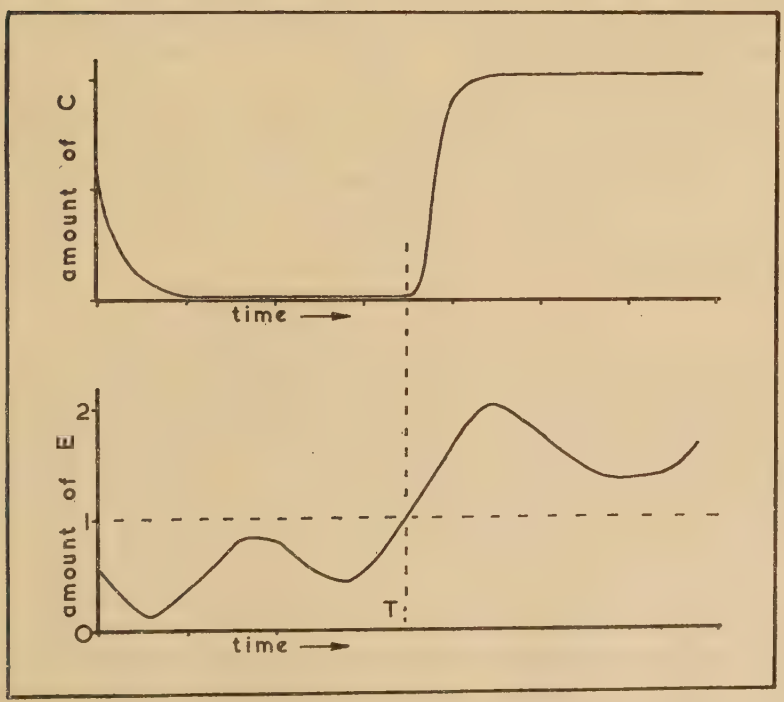

FIG. 2.—The effect on the amount of C of changes in the amount of E. (The time-scale is the same in both).

values of *C* is only two. Thus, when the amount of enzyme is over a critical amount (given as one arbitrary unit in the diagram), the quantity of *C* rises to a maximum, but if the system contains less than this critical amount of enzyme, then the quantity of *C* falls to zero. If the amount of enzyme undergoes variations which do not cross the critical amount, then the effect on the quantity of *C* is only to alter the velocity with which *C* attains the upper or lower limit, but the limit to which *C* is tending does not alter. It will be noted that at these limits *A* is being converted either wholly into *B* or wholly into *C*.

It is, therefore, possible to have a metabolic system controlled by an enzyme such that if the amount of enzyme present is more than a certain amount, then substance *A* is converted wholly into *C*, while if the amount of the enzyme is less than this amount, then *A* is converted wholly into *B*. So an enzyme, affecting primarily only a velocity may yet cause a metabolic process to change to an " all or none " degree.

The same system and the same essential fact can be shown from another aspect. Such a system shows the phenomenon of " threshold." For if we make the amount of enzyme vary, watching the effect on the quantity of *C*, we shall get something like Fig. 2. We start with the amount of enzyme lower than our arbitrary one unit and *C* therefore falls towards zero—that is, *C* disappears from the system. After this, *C* stays absent no matter how the amount of enzyme fluctuates, provided the critical amount of one unit of enzyme is not exceeded. But if, as at time *T*, this amount is exceeded, then *C* will be formed and will increase to the maximum. The enzyme's critical amount of one unit is therefore a threshold for the enzyme's effect on the quantity of *C* present.

It should be noted that were we observing the system to test whether the enzyme had any effect on *C*'s production, then if we added less than the critical amount of enzyme we would get no change in the amount of *C*. We might deduce that the enzyme had no effect at all on *C*'s production, but not until the enzyme had been increased beyond the critical amount would the true effect be revealed.

* * * * *

Finally, has this demonstration any clinical or therapeutic import ? I will conclude by giving four instances where this knowledge may be of use :

The first is in questions of aetiology. It is sometimes thought that a metabolic disturbance, if due to lack of a hormone, vitamin or enzyme must produce symptoms approximately in proportion to the lack of the essential substance concerned. I have tried to show that this proportionality is not at all necessary : that an essential substance can have a critical amount for the production of its characteristic effect. Lack of an essential substance may cause no effect if the lack is only moderate, but when the lack becomes more marked the abnormal symptoms may appear suddenly and in almost maximal degree. Conversely, in such a state the replacement of the missing hormone or vitamin may produce a result only when the amount given exceeds some critical amount.

The second aspect also concerns aetiology. Knowing that enzymes affect directly only the velocities of metabolic processes, we are apt to think that lack of a hormone, vitamin or enzyme can lead only to a mild slowing of the metabolic processes, a change from a normal to an abnormal process not being possible. I have tried to show that this is false. There is no limit to the degree or type of change which can be induced by alteration in the amount of an enzyme.

Thirdly, the method I have used above leads also to a clear understanding of the question of whether the deviation of metabolic processes can be irreversible. But an attempt to discuss this adequately would exceed the limits of this paper.

Finally, the meaning of this knowledge in therapeutics is clear. If we have some reason to suspect that a given syndrome is due to lack of some hormone or vitamin or enzyme, then finding that small doses produce absolutely no effect should not be considered as proof that the substance is unrelated to the syndrome. A further increase of the dose or a more effective method of administration may yet cause a sudden and marked improvement. Treatment has, of course, often been guided by the possibility of this event. Here I have tried to demonstrate the underlying principle.

Summary.

Enzymic systems are responsible for most, if not all, of the body's metabolic processes, and hormones probably control these processes by affecting specific enzymes. Enzymes control only the velocities of chemical reactions, but this does not imply that the results of enzymic alteration are limited to quantitative changes only. On the contrary, it is shown that changes in the concentrations of enzymes and hormones may lead, as the concentrations pass certain critical levels, to changes sudden and catastrophic.

Some therapeutic implications are discussed.

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THE 700TH ANNIVERSARY OF BETHLEM.

By DUNCAN WHITTAKER, M.A., M.R.C.S., L.R.C.P., D.P.M.

THIS year marks the seven hundredth anniversary of the founding of the House of Bethlem. Seven hundred years! It takes us back to the very beginnings of English culture. Much in our constitution that we hold dear dates from this thirteenth century, which saw the foundation of Bethlem. In 1215 King John signed the Magna Carta, and in 1265 Simon de Montfort summoned not only the knights of the shire, but for the first time two representatives from each of the chartered boroughs, the precursor of the House of Commons. It was between these two dates on the Wednesday after the Feast of St. Luke the Evangelist, which in the year 1247 fell on 23 October, that Simon FitzMary, a citizen of London, signed the deed-poll which founded this hospital. He had given and granted to God and the church of St. Mary of Bethlem all that land of his which he had in the parish of St. Botolph without Bishopsgate London, to wit, all that he had or might have there, in houses, gardens, orchards, fish-ponds, ditches, marshes and all other things appertaining thereto as defined by their boundaries. These extended in length from the king's highway on the east to that ditch on the west which was called Depeditch, and in breadth to the land which belonged to Ralph Dunning on the north and to the land of St. Botolph's church on the south. The gift was for the formation of a priory under the rule and order of the church of Bethlem, the brothers and sisters to wear publicly upon their copes and mantles the badge of a star. He further declared in the deed poll that: "For the greater security of this gift I have placed myself and mine outside the said property, and I have solemnly put in actual possession of it, and have handed over the possession of all things aforesaid to the lord Godfrey of the family of the Prefetti of the city of Rome, at this time bishop-elect of Bethlem (as by our lord the pope confirmed) and at this time actually in England, in his own name, and in that of his successors, and in the name of the chapter of the church of Bethlem. And he has received possession of the said property, and has entered upon it in the form prescribed."

We know little of the first century of our history, but we do know that during this period there occurred two of the worst famines in English history. The first lasted from 1257 to 1259. It was due to a succession of bad harvests, following either cold and backward springs or wet autumns. But the scarcity and dearness of corn would hardly have had such disastrous effects if the country had not been short of circulating coin, which had been drained by levies for the Roman See and its use in bribing electors in the king's brother's candidature for the crown of the Holy Roman Empire. Sixty shiploads of grain were

brought over from Holland and Germany to feed the starving Londoners. The famine was of course followed by a pestilence. The next famine occurred in 1315–1316. Measures were taken then, as now, to restrict the amount of grain turned into malt. In London 55 persons, children and adults, were crushed to death in a scramble for bread doled out at the Blackfriars.

In the third year of the reign of Edward III, 1330, the house was described as a hospital in a licence granted by the king to the master and brethren to collect alms in England, Ireland and Wales. There was no mention in this record of sisters or canons, but, of course, the use of the term hospital was very broad at this time. In the same year the Archbishop of Canterbury wrote to the clergy granting an indulgence of 40 days to all who had "contributed, bequeathed, or in any manner assigned any of their goods in contribution and support of the brothers, proctors, and other poor infirm, dwelling in the said hospital." By the year 1346 the priory appears to have been so poor that the Master, John Matthew de Norton, and the brethren petitioned the Mayor and Aldermen of the City of London to be received under their protection. An agreement was made that two Aldermen should be chosen each year, one by the Mayor and Aldermen and the other by the Master and brethren of the house. These were, in effect, the first governors, and apart from supervising the master and brethren they instituted a biannual audit.

In 1348 the Black Death struck England. It was believed to have started in China, and by 1348 it had spread all over the shores of the Mediterranean. By August it had arrived at Melcombe Regis in Dorsetshire. It appeared in London on 1 November. April the following year was the worst month, judging by the number of wills proved, and by Whitsun it was on the decline. In London the highest mortality was over 200 a day, which, according to Creighton, must have represented a total mortality of 20,000, or half the population. The whole of England lost a third to half its inhabitants and did not recover until the reign of Elizabeth. This bubonic plague was the same as the later great plague of London, which occurred in Pepys's time. There was a second epidemic in 1361, a third in 1368–1369, a fourth in 1375, a fifth in 1382, and a sixth in 1390–91. That Bethlem also suffered from the plagues is apparent from the fact that the Pope granted a petition from the hospital at Avignon, 1363.

In 1375 in the forty-eighth year of the reign of Edward III, Bethlem was seized by the Crown as an alien priory. Disputes afterwards arose between the Crown and the City as to their right to appoint the master of Bethlem, but the Crown triumphed, and Richard II, Henry IV, Henry VI and Henry VIII insisted upon and exercised their right of presentation.

The date at which Bethlem first housed mental patients is not known to any degree of accuracy. Stow, in his *Survey of London* states: "Then had ye 'the chapel of our Lady called the Pew with an house, wherein sometime were distraught and lunatick people, of what antiquity founded, or by whom, I have not read, neither of the suppression, but it was said that sometime a king of England, not liking such a kind of people to remain so near his palace, caused them to be moved farther off to Bethlem without Bishopsgate London, and to that hospital the said house

by Charing Cross doth yet belong." The Royal Commission of 1632 stated: "When the hospital was first employed to the use of distracted people appeareth not. The first mention of it to be employed so was in the beginning of the reign of Richard II." This would make it about 1377. We know for certain that six men who were of unsound mind were confined there in 1403, as the Royal Commission of that date mentions sex homines mente capti as well as instruments of restraint. It is to this Commission, formed to enquire into the defalcations of the porter, one Peter Taverner, that we owe the preservation of a copy of our foundation deed.

In the year 1538, between the act for the suppression of the lesser monasteries and the final dissolution, the Mayor, Aldermen and Commonalty of the City of London petitioned the king for three hospitals and an abbey, not for priests and monks, who, they stated, presumably to get on the right side of the king, had been living carnally and had done "nothing regarding the miserable people lying in the street, offending every clean person passing by the way with their filthy and nasty savors," but that "a greater number of poor and sick persons should be refreshed, maintained, healed, and cured, frankly and freely by physicians, surgeons and apothecaries, who should have stipends to attend for that purpose, so that impotent persons should be relieved thereby and sturdy beggars, not willing to labour, should be punished, and so few or none be seen abroad to ask alms." No attention was paid to this attempt to transfer the administration of the revenues of several establishments to the corporation of the City of London until 1546, and finally on 13 January, 1547, in the 38th year of his reign, Henry VIII granted by royal charter to the Mayor, Commonalty and citizens of London, St. Bartholomew's Hospital, to be called "The House of the Poor, in West Smithfield, near London, of the Foundation of King Henry VIII," and the house and hospital called Bethlem, situate without and near Bishopsgate of the said City of London. The charter of Henry VIII was confirmed by another granted by Charles I, dated 1638. In 1553 Edward VI granted by Royal Charter the three hospitals, Christ's, Bridewell and St. Thomas the Apostle to the Mayor, Commonalty and citizens of the City of London. At a general court, held at Christ's Hospital, 27 September, 1557, separate governors and four several treasurers were appointed for the hospitals of Christ's, St. Thomas, St. Bartholomew, and Bridewell, to which latter hospital the house of Bethlem, though totally distinct in its object, was annexed, one treasurer and the same governors being appointed for both. The union between Bridewell and Bethlem has continued to the present day, and was confirmed by the Act 22, George III. By an order of Common Council, 1587, it was laid down that the unemployment problem of the time should be dealt with in the following way:

"The stout and strong vagabonds to labor in scowring the towne ditches and their diet to be provided for a time by the governors of Bridewell until further orders be taken.

"The sick, sore and lame, which are cureable, to be sent to the hospitals of St. Bartholomew's and St. Thomas.

"The small children, which are infants and not able to work, and born in the city, to be kept in the Christ Hospital.

"The women and others of small strength to be employed in the work of the house of Bridewell, or otherwise, at the discretion of the governors.

"And such and so many as have not been resident in this city and liberties aforesaid, to be conveyed from constable to constable according to the statute."

Pope, in the "Dunciad," mentions Bridewell:

> "This labour past, by Bridewell all descend,
> (As morning prayer, and flagellation end)
> To where Fleet-ditch with disemboguing streams
> Rolls the large tribute of dead dogs to Thames."

He makes a note to the effect that it was between eleven and twelve in the morning, after church service, that criminals were whipped in Bridewell.

As early as 1603, when Stow published his *Survey of London*, the surroundings of Bethlem appear to have been none too savoury. He writes of St. Botolph's Church, mentioned in our foundation deed: "The parish church of St. Buttolph without Bishopsgate, in a fair churchyard, adjoining to the town ditch, upon the very bank thereof, but of old time inclosed with a comely wall of brick, . . .

"Now without this churchyard wall is a causeway, leading to a quadrant, called Petty France, of Frenchmen dwelling there, and to other dwelling houses, lately built on the bank of the said ditch by some citizens of London, that more regarded their own private gain than the common good of the city; for by means of this causeway raised on the bank, and soilage of houses, with other filthiness cast into the ditch, the same is now forced to a narrow channel, and almost filled up with unsavoury things, to the danger of impoisoning the whole city.

"Next unto the parish church of St. Buttolph is a fair inn for receipt of travellers; then an hospital of St. Mary of Bethlehem, founded by Simon FitzMary, one of the sheriffs of London, in the year 1246 (he got the date wrong), he founded it to have been a priory of canons, with brethren and sisters; and King Edward III granted a protection, which I have seen, for the brethren, Miliciae beatae Mariae de Bethlem, within the city of London, the 14th year of his reign. It was an hospital for distracted people . . . the church and chapel whereof were taken down in the reign of Queen Elizabeth, and houses built there by the governors of Christ's Hospital in London. In this place people that be distraight in wits are, by the suit of their friends, received and kept as afore, but not without charges to their bringers in. In the year 1569, Sir Thomas Roe, merchant-tailor, mayor, caused to be inclosed with a wall of brick one acre of ground, being part of the said hospital of Bethlem; to wit, on the west, on the bank of Deep Ditch, so called, parting the said hospital of Bethlem from the More field: this he did for burial and ease of such parishes in London as wanted ground convenient within their parishes. The lady his wife was there buried, (by whose persuasion he inclosed it), but himself, born in London, was buried in the parish church of Hackney.

"From this hospital northward, upon the street's side, many houses have been built with alleys backward, of late time too much pestered with people

(a great cause of infection) up to the bars." The earliest description of the hospital which has been found is in an entry made in the muniment book, 1632 :

" Bethlem, wherein the poor distracted persons are kept.

" One messuage newly builded of brick at the charge of the said hospital, containing a cellar, a kitchen, a hall, four chambers, and a garret, being newly added unto the old rooms.

" Item, the old house, containing below stairs a parlour, a kitchen, two larders, a long entry throughout the house, and 21 rooms wherein the poor distracted people lie, and above the stairs eight rooms more for servants and the poor to lie in, and a long waste room now being contrived and in work, to make eight rooms more for poor people to lodge where they lacked room before."

In the minutes of a court held in 1644 it stated that 44 lunatics at least were kept continually at Bethlem with diet and physic and other relief, and that the rents and revenues did not amount to two-thirds of the yearly charge.

The first or medieval Bethlem is coming to its end. The second hospital in Moorfields was started in 1675 and completed in July, 1676. It is a convenient moment to ask what views were held on medicine and physiology during these first centuries of Bethlem's history. We could do worse than go to John Donne, who flourished, if such a word can be used of that gloomy dean, during the early part of the seventeenth century :

" Thou art to narrow, wretch, to comprehend
Even they selfe : yea though thou wouldst but bend
To know they body. Have not all soules thought
For many ages, that our body' is wrought
Of Ayre, and Fire, and other elements ?
And now they think of new ingredients,
And one Soule thinks one, and another way
Another thinks, and 'tis an even lay.
Knowst thou but how the stone doth enter in
The bladders cave, and never breake the skinne ?
Know'st thou how blood, which to the heart doth flow,
Doth from one ventricle to th'other goe ?
And for the putrid stuffe, which thou dost spit,
Know'st thou how thy lungs have attracted it ?
There are no passages, so that there is
(For ought thou know'st) piercing of substances.
And of those many opinions which men raise
Of Nailes and Haires, dost thou know which to praise ? "

When we come to the more nearly psychiatric angle, we have the hypothesis of vapors :

" But what have I done, either to breed, or to breath these vapors ? They tell me it is my Melancholy ; Did I infuse, did I drinke in Melancholy into my selfe ? It is my thoughtfulnesse ; was I not made to thinke ? It is my study ; doth not my calling call for that ? I have done nothing wilfully, perversely toward it, yet must suffer in it, die by it ; There are too many Examples of men, that have bin their own executioners, and that have made hard shift to bee so ; Some have always had poyson about them, in a hollow ring upon their finger, and some in their pen that they used to write with ;

some have beat out their braines at the wal of their prison, and some have eate the fire out of their chimneys ; and one is said to have come neerer our case than so, to have strangled himself, though his hands were bound, by crushing his throat between his knees ; But I doe nothing upon my selfe, and yet am mine owne Executioner. And we have heard of death upon small occasions, and by scorneful instruments ; a pinne, a combe, a haire, pulled, hath gangred, and kill'd ; But when I have saide, a vapour, if I were asked again, what is a vapour, I could not tell, it is so insensible a thing ; so neere nothing is that that reduces us to nothing."

The last years of the old hospital saw the Great Plague of 1665, and the Fire of London in 1666, which however spared Bishopsgate. Pepys made a note in his diary 19 February, 1669, that he spent the day at the office and the young ones went to Bedlam. This habit of treating the hospital as a peep-show continued well into the eighteenth century, and in Hogarth's painting of 1735 (the last of The Rake's Progress) a lady and her maid are shown going round the male side, the lady modestly hiding her face behind her fan, while the maid describes to her the appearance of an almost naked male patient.

The second Bethlem in Moorfields was a building of considerable architectural merit, as one can see from the many prints of it still in existence. It was said to have been built in imitation of the Tuileries. It was described in the 1754 edition of Stow's *Survey* as consisting of two galleries over the other, 193 yards long, 13 feet high, and 16 feet broad, not including the cells for the patients, which were 12 feet deep. These galleries were divided in the middle by two iron gates separating the male and female sides. These gates and the cells appear in Hogarth's celebrated print. It was of this building that Gay wrote :

> " Through fam'd Moorfields, extends a spacious seat ;
> Where mortals of exalted wit retreat ;
> Where, wrapp'd in contemplation and in straw,
> The wiser few from the mad world withdraw."

Two wings were later added, one in 1725, the other in 1733, for male and female incurable patients. The Moorfields hospital was in continuous use until 1815.

Pope not only makes a number of references to this hospital, but also mentions one of the physicians of the time :

> " And when I flatter, let my dirty leaves
> (Like journals, odes, and such forgotten things
> As Eusden, Philips, Settle, writ of kings)
> Clothe spice, line trunks, or fluttering in a row,
> Befringe the rails of Bedlam or Soho."

In another imitation of Horace he wrote :

> " Sure I should want the care of ten Monroes,
> If I would scribble rather than repose."

Actually there were four Monros at Bethlem, to whom I will refer later.

In 1800 the architects reported the hospital to be in an insecure condition, and in 1815 the patients were transferred to the third Bethlem in St. George's Fields, which was begun in 1812. This building with the dome, which was completed in 1846, was in use until 1930, when we moved to Monks Orchard. The central part of the old hospital including the dome is all that is now left and serves as the Imperial War Museum.

It is difficult, when covering seven centuries in half-an-hour, to give more than an impressionistic picture, but there are several examples of the impact of Bethlem on the outer world which are worth mentioning. Langland apparently considered the wandering monks of Bethlem to be a nuisance as he wrote :

"A peril to the popes and prelates that he maketh, that bear bishops names of Bedleem and Babiloigne, that hop about in England to hallow men's altars, and creep about among the clergy, hearing confessions, which they have no right to do."

Later there was the nuisance of the Bedlam beggars, who pretended to be ex-patients. You will remember how the fleeing Edgar in *King Lear* cried :

" I heard myself proclaim'd ;
And by the happy hollow of a tree
Escaped the hunt. No port is free, no place,
That guard and most unusual vigilance
Does not attend my taking. Whiles I may 'scape
I will preserve myself ; and am bethought
To take the basest and most poorest shape
That ever penury in contempt of man
Brought near to beast : my hair I'll grime with filth,
Blanket my loins, elf all my hair in knots,
And with presented nakedness out-face
The winds and persecutions of the sky.
The country gives me proof and precedent
Of Bedlam beggars, who with roaring voices
Strike in their numb'd and mortified bare arms
Pins, wooden pricks, nails, sprigs of rosemary ;
And with this horrible object, from low farms,
Poor pelting villages, sheep-cotes and mills,
Sometime with lunatic bans, sometime with prayers,
Enforce their charity. Poor Turlygod ! poor Tom !
That's something yet : Edgar I nothing am."

Another impact of Bethlem on the outer world, altogether beneficial this time, was the patronage by the second Monro, Dr. Thomas Monro of the brilliant English school of water colourists, probably, outside the Chinese, the greatest water-colourists the world has seen. Alexander Cozens, who had come from Russia to England and taught drawing at Eton, had a son J. R. Cozens, who had a complete nervous breakdown and died under Dr. Monro's care in 1799. According to Faringdon, " Turner and Girtin told us they had been employed by Dr. Monro three years to draw at his house in the evening . . ." Girtin drew in outlines and Turner washed in the effects. They were employed chiefly in copying the outlines and unfinished drawings of Cozens, etc., of which copies they made finished drawings. Girtin, Turner, Cotman, Varley and de Windt all worked at Dr. Monro's, copied Cozens and stimulated one another, yet retained their individuality.

The first physician to be connected with the hospital was John Arundell, not apparently in his capacity as a physician, but as master of the hospital in 1457–1458. Previously in 1453 Henry VI had lost his reason, memory, and powers of speech and movement, and Arundell, who was his chaplain, confessor, and first physician, was authorized with other physicians and surgeons to administer head purges, and to shave the king's head, and to give him baths.

From 1619–1634 Hilkia Crooke was physician and Keeper, but he appears to have been largely an absentee placeman. From 1634 a regime was instituted in which there was a non-resident physician, an apothecary and a visiting surgeon. Of the earlier non-resident physicians, the best known is Edward Tyson, whose name is commemorated in our present acute block. He was physician from 1684–1708. The remarkable family dynasty of Monro's, in which son followed father for four generations, lasted from 1728–1853. A descendant of this family was still a licensee of Brooke House up to its bombing in the late war. Thomas Monro, the art patron, has already been mentioned. Henry Monro, the son of the last Monro, did not get on the staff but was trained in the wards of the hospital. In 1851 he published *Remarks on Insanity, its Nature and Treatment.* In this book he proposed the hypothesis of positive and negative symptoms which Hughlings Jackson adopted with acknowledgments, and elaborated so successfully. So that the family, which enjoyed the fruits of office for so long, helped materially to contribute to the foundations of modern neurology.

John Haslam, apothecary to the hospital, in his *Observations on Madness and Melancholy*, 1798, described a case of general paralysis of the insane without recognizing it as a specific entity.

In 1853 the custom of having non-resident physicians ceased, and William Charles Hood became the first resident physician as opposed to resident apothecary. He raised the social standard of the patients, and was instrumental in having the criminal patients removed. The present type of regime is a direct continuation from his day.

While many things have been improved since those days, it is sad to recall that in 1823 the butter ration was 16 ounces per week, that the patients had half a pound of corn beef on Sundays and a roast on two other days of the week. Excellent table beer was served without any stint of allowance, but the average quantity did not exceed a quart per patient per day.

A tendency to undue reminiscence is a sign of approaching senility. Old we may be, senile we are not, so I will make an end. "Do on then fast, I pray thee. Look now forwards and let the backwards be."

CEREBRAL SYMPTOMS IN THROMBO-ANGIITIS OBLITERANS.

By David Perk, M.D., D.P.M.,
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Von Winiwarter, in 1879, published his pathological findings in a case in which there was obliteration of the vessels of the leg due, as he considered, to a proliferative process in the intima, that is to say, an "endarteritis obliterans." Other views on the pathology came to be propounded, notably that of van Manteuffel, who considered that consequent upon arteriosclerosis of the popliteal artery a white thrombus formed, which, spreading peripherally and becoming organized, produced the picture of an obliterative endarteritis. Twenty-five years after Winiwarter's paper Buerger published his observations based on 30 cases, with pathological studies on the vessels obtained from eleven amputated limbs. He disagreed with the views of both von Winiwarter and von Manteuffel. He found that besides an extensive obliteration of the larger arteries and veins there was a varying degree of peri-arteritis and arteriosclerotic thickening of the vessel wall, and concluded that the condition was a thrombotic process occurring in the arteries and veins, followed by organization and canalization, and not an obliterating endarteritis. He absolved the intima from any "considerable role in the genesis of the thrombotic process," and attributed the thickening of the intima and the cellular infiltration and vascularization of the media and adventitia to the agency producing the coagulation of the blood and to the changes in the thrombus itself. He saw the final lesion as a vessel obliterated by dense connective tissue, canalized, together with some residual cellular infiltration and capillarization of the media and greater or less thickening of the adventitia and periarterial tissues, the thrombus having disappeared in the course of the development of this final result. He proposed the term "thrombo-angeitis obliterans" for the condition, and with the general adoption of the term Buerger's name came to be linked with it.

Some authors have considered that the condition is inflammatory in nature. Scheinker, however, states that he found no inflammatory changes either within or surrounding the vessels. He considered that this feature helped to distinguish thrombo-angiitis obliterans from periarteritis nodosa, with which, in his opinion, some observers were apt to confuse the condition. In periarteritis nodosa marked inflammatory changes were to be found extending through the entire vessel wall.

He describes thrombo-angiitis obliterans in the cerebral vessels as beginning with small intramural haemorrhages. The extravasated intramural blood,

confined to the subendothelial tissue of the intima and the muscularis, detaches the endothelial lining and pushes it into the lumen of the affected vessel. The subendothelial cells of the intima, and to a lesser extent the muscularis, undergo necrosis. Later, with the absorption of the extravasated blood, there is a fibroblastic proliferation in the subendothelial tissue, followed by a proliferation of connective-tissue fibrils, ending in the formation of scar-tissue. The thickening of the vessel wall leads to narrowing of the lumen of the affected vessel, and total occlusion occurs with thrombus formation induced by degenerative changes in the endothelium. He found recanalization in the older lesions. The vascular lesions in his case were confined to the medium sized veins and the smaller arteries. Larger blood vessels and capillaries were not usually affected. There was destruction of the nervous tissue supplied by the affected vessels.

He quotes Marchesani, Stander and Ludwig, who observed recurrent haemorrhagic extravasation into the retina and vitreous humour associated with vascular lesions of thrombo-angiitis obliterans in the extremities and other parts of the body as parallel instances of haemorrhage into the vessel walls of the brain which, he believes, is a recurrent phenomenon. He considers these haemorrhages set up reversible disturbances of the vessel walls—spasm and paralysis—and when these are repeated or protracted the reversible changes become permanent. The remittent character of the earlier cerebral symptoms he ascribes to the presence of reversible changes. In support of this contention he quotes Foerster and Guttmann, who had observed transient vasoplastic phenomena in the retinal arteries ophthalmoscopically in a typical case of thrombo-angiitis obliterans. Hausner and Allen have offered an alternative explanation for the remission of symptoms in the rapid development of collateral circulation after thrombosis.

Bauer in 1935 drew attention to Winiwarter's prior claim to the distinction, and the condition is sometimes referred to in the literature as Winiwarter-Buerger's disease. The credit for recognizing that cerebral symptoms may occur in the course of thrombo-angiitis obliterans conceded by some to Foerster and Guttmann, who called attention to this observation in 1933, is challenged by Bauer, who points out that they were preceded in this by Cserna in 1926, Friedman in 1931, and Bauer himself in association with Recht in 1932. There were, in fact, others besides those mentioned by Bauer. Hausner and Allen mention Merkelbach (1933), Livingston (1933), Jäger (1932), Lilienthal and Barron (1929), Stahnke (1928), Lewis (1927), Buerger (1924). There is not, however, an abundance of references to the cerebral manifestations in Buerger's disease in the literature, and as Scheinker observes, there are even fewer histopathological studies of the brain and cerebral vessels to support the clinical observations. Apart from his own studies (also in association with Sträussler and Friedman (1937)), he mentions by name those of Spatz (1935) and of Lindenberg (1939).

Hausner and Allen, reviewing the literature in 1938, found 23 cases recorded of involvement of the cerebral arteries in association with thrombo-angiitis obliterans of the extremities. Their review was not, however, an exhaustive one, and there are a good many more cases available in the literature up to

1938. Scheinker mentions that in the 7 years 1937–44 only 3 cases of cerebral thrombo-angiitis obliterans reached the laboratory of neuro-pathology, Cincinnati General Hospital. Hausner and Allen found 11 cases of cerebral involvement in a group of 500 with thrombo-angiitis obliterans of the extremities at the Mayo Clinic, giving a percentage incidence of 2·2.

In their review of the literature Hausner and Allen found that the commonest cerebral symptoms were transient hemianopia and transitory, constant or recurrent hemiplegia. In their own 11 cases the duration of the peripheral disease varied from 5 months to 20 years. The cerebral lesion preceded the peripheral symptoms by 1 to 14 years in 3 cases; in the others it followed them. The outstanding symptom was transient or permanent hemiplegia; other symptoms were transient confusion, disorientation, aphasia, loss of memory. Hemianopia was present in 2 cases, and cleared up in 1 case following sympathectomy. One of their cases had had recurrent mental disturbances for 17 years prior to the onset of the thrombo-angiitis obliterans, but Hausner and Allen do not claim a common pathology for the two conditions. In some of the cases recorded by other authors a connection between mental changes and thrombo-angiitis obliterans can be clearly discerned. In the case reported by Scheinker, for instance, there can be little doubt that the mental disturbance in the form of a sudden alteration of behaviour on the part of the patient, and the first symptom manifested by him, was occasioned by the same condition that 3 months later produced various cerebral symptoms, and 6 months later still a sudden right hemiplegia with motor aphasia. Scheinker confirmed the diagnosis as that of thrombo-angiitis obliterans by post-mortem histological study of the cerebral vessels. It will be noted, however, that there is no report of peripheral vascular obstruction having occurred. The fuller clinical history of the case is as follows:

The patient, a policeman, aged 43, suddenly left his job and home and went to another town. Three months later localizing cerebral symptoms were noted: the patient began to have attacks of weakness and myotonia affecting muscles of face, speech, deglutition and arms; also attacks of numbness, dizziness and generalized weakness. They occurred frequently—as often as twice a week—preceded by twitching of eyes. Nine months after the commencement of symptoms he suddenly developed a right hemiplegia with motor aphasia and died 5 weeks later.

Guttmann's case is an instance where the mental symptoms followed the manifestations of the disease in the extremities. Though the age of his patient, 61 years, suggests that the mental and cerebral symptoms might have been produced by cerebral arteriosclerosis, especially in view of the high blood pressure recorded, the nature of the pathological condition in the cerebral vessels was confirmed post-mortem as that of thrombo-angiitis obliterans. His patient had suffered from intermittent claudication for 21 years, and in the year prior to examination, when it was noted that pulsation was absent in the extremities and accompanied by acrocyanosis, the patient had suffered from confusion and excitement. There were other evidences of cerebral involvement such as slight paresis of facial expression, increased reflexes, amnestic aphasia and apraxia. After coming under treatment, and with the

improvement of the neurological symptoms, the patient developed a paranoid psychosis.

The literature provides evidence that any neurological symptom may be produced by thrombo-angiitis obliterans of the cerebral vessels: muscular spasms ranging from tics to epileptiform convulsions, palsies ranging from weakness to complete paralysis, either localized to a group of muscles, commonly in the face or in an extremity, or affecting half the body (hemiplegia), sensory disturbances, commonly hemianopia and numbness, affections of speech (aphasia), memory (impoverishment) and higher cerebral functions (apraxia), and interruption of consciousness (unconsciousness). In addition, mental symptoms may occur, though less frequently than neurological symptoms, ranging from transient confusion or excitement to full-fledged psychoses. Neurological and mental symptoms may precede, though more commonly they follow manifestations of the disease in the extremities and other parts of the body, commonly the heart, mesenteric vessels and eyes. In the earlier manifestations the cerebral symptoms tend to transcience and recurrence, later to permanence.

Several authors (Meves, Hausner and Allen), alluding to the long interval that may occur between the onset of cerebral symptoms when they precede the manifestation of the disease in the extremities and peripheral symptoms, point the need to bear thrombo-angiitis obliterans in mind as a possible diagnosis for cases of cerebral vascular disease occurring in the absence of a presenting aetiological background. This applies especially to cases occurring in early adult life. Later, sclerosis of cerebral vessels offers an alternative explanation; and a mixed pathology—as, for example, the presence of both peripheral thrombo-angiitis obliterans and cerebral arteriosclerosis—may account for the association of cerebral and peripheral symptoms.

The case described in the following notes came to the present author's attention when the man's clinical documents were under scrutiny for consideration of his claim to a pension.

The patient enlisted in the Royal Navy in November, 1940, in sound condition, and did not come under medical observation until 3 years later, when he was admitted into the sick bay of his ship for inflamed areolar tissue of the right great toe. He was then 29 years of age. There was inflammation and pain of the toe with slight inguinal adenitis. He reported that he had dropped something on his foot, breaking the skin of the toe. The inflammation quickly subsided under treatment, and the patient was discharged back to duty after 3 days. He did not again come under medical care until 11 months later, when his behaviour in the ship's galley led to his referral to a psychiatrist. Apparently normal and giving satisfactory service up to the time of the galley scene, he had sat up reading all night, and in the morning prepared breakfast in a slapdash manner, and placed notices outside the galley in reference to the breakfast that the troops could "take it or leave it." On admission to hospital he was found to be elated, and within a few hours he became extremely noisy and restless, throwing bedding about, talking incessantly and incoherently, breaking into song, and showing aggression to staff when being attended to. Sustained conversation with him was impossible because of flight of ideas running into incoherence. His talk showed a grandiose vein with referencing of events to himself—the war was being fought on his account, he started the civil war in Greece, etc. He was disorientated to time, place and person. Physical examination was negative, other than that it

was noted he had flat feet with hallux valgus and plantar callosities. There were apparently no signs of vascular obstruction in the legs at that time.

Information from the family revealed that an elder brother had committed suicide and that the patient had recently suffered several bereavements—a brother was killed in Sicily and a sister and her child in a flying bomb incident—which, it was stated, had upset him considerably. Though not a heavy drinker, he had recently been drinking more than usual.

When after 3 weeks of continued restlessness, noisiness and destructiveness and incoherence he became more rational he confirmed the above particulars given by the family, and revealed that for some days he had felt worried about his family and blamed himself for his failure at work, and was restless and sleepless. It would seem then that though his mental state did not appear as suddenly as the earlier reports made out, it developed rapidly, probably over a few days. He also recalled some of the delusional ideas that entered his mind during the acute phase—that he could make a fortune at the "dogs," at which he was a regular attender, that he was being televised through a vent in the room—and affirmed that he had had auditory hallucinations. Though rational, correctly orientated and in full contact with his environment, he was euphoric and circumlocutory in conversation. The improvement lasted about 5 days, when he relapsed by rapid degrees into an acute manic condition (wildly elated, constantly talking and manifesting flight of ideas and extreme distractibility, too busy to eat and taking little fluid or food, voice hoarse) which exhausted him, so that he collapsed, pulseless, after about 7 days. He was comatose for 2 days, during which time the pulse was 110, his lips were cyanotic and his heart sounds were noted as "weak but closed, with tic-tac rhythm. Aortic second sound slightly accentuated." It was now observed for the first time that the toes of his feet were all cyanotic and showing early dry gangrene. Pulmonary consolidation was not found at any time, and there was no dyspnoea. When he regained full consciousness he made no complaint of pain in the feet or elsewhere. He remained cyanosed, and his heart sounds were weak for 4–5 days after the collapse. The dry gangrene of the toes continued to advance, oedema of dorsum of both feet up to and including the ankles developed and clear blisters formed on the dorsum of the right foot. There was good capillary circulation above the mid-tarsus and no palpable thrombosis. The posterior tibial and dorsalis pedis pulses of both legs were absent. The demarcation developed progressively at the tarso-metatarsal joints, and after three weeks sepsis developed at the line of demarcation. The sepsis cleared in the left foot after a few days but was followed by sloughing of the toes of the right foot. Mentally there was no change. From the time patient recovered from the comatose state he was very restless, deluded, over-talkative and sleepless when not under sedation. It was $2\frac{1}{2}$ months before there was again mental improvement, and again it only lasted about 5 days. Concurrently with the succeeding relapse he had the first major epileptic fit. Two days prior to the fit when his B.P. was taken it registered 116/72, and blood examination, performed after the fit, gave negative Wassermann and Kahn reactions.

The mental symptoms, maniacal in character, grew rapidly more severe until patient was filthy in habits, incontinent of urine and faeces, confused, hallucinated, resistive and impulsive, and after 3 weeks he collapsed again. His pulse counts over the next 24 hours were 108, 104, 114, 106. This time he regained consciousness after 4 hours. His heart sounds also improved rapidly. Some few days before he collapsed his big right toe sloughed off. Then followed a fortnight's calm and rationality terminated by a further relapse and eventual collapse—for the third time. On this occasion the pulse was no more than 90, and the patient improved physically more rapidly than previously. For the next 3 months, except for several brief intervals of comparative tranquillity he continued restless, confused and occasionally aggressive and impulsive. His maniacal condition did not, however, again reach the earlier intensity, and towards the end of this period a mild depressive phase was noted for the first time. This phase lasted about a week, and was succeeded by a recurrence of mania and eventual collapse (fourth time). There followed alternate depressive and manic phases for about a fortnight, and the patient then gradually slipped into a quiet, confused, perplexed state with rambling, occasional thought-blocking and auditory hallucinations, punctuated at times by impulsiveness (window-smashing), aggressiveness, brief attacks of acute excitement with hallucinations and less frequently by depressive

phases (attempted suicide in one). At this stage the condition began to have the look of a confusional state. It was now 12 months since his condition began. He had during the year lost all the toes of his right foot and three of the left foot. He had had altogether 6 epileptic fits, and on one occasion he was noted to complain of diplopia (it was attributed to the sedatives he was having). For about 3 months the mental condition continued as described. Improvement then set in. This proceeded uninterrupted for about a month—except that for a day he passed loose stools containing blood and mucus, but negative for the dysenteric and typhoid groups of organisms—when he was noted to have difficulty in articulating and expressing himself and to be slow of cerebration. At this stage his brother took him out of the civil mental hospital where he had been a patient for the past 4½ months, and no further particulars are available. Altogether the patient had been under continuous medical observation for 16½ months.

Commentary: It provides some indication how comparatively little known is the occurrence of cerebral manifestations in thrombo-angiitis obliterans that this case was, in the 16½ months that it was under observation, variously diagnosed as schizophrenia, mania, manic-depressive psychosis, epileptic psychosis, all as primary conditions, at the same time that the condition of the feet was correctly diagnosed as due to thrombo-angiitis obliterans. It may, of course, be that the mental condition was unconnected with the vascular one—other authors have warned against too readily assuming a connection between the two—but the occurrence of other cerebral manifestations such as fits, diplopia, dysarthria, the earlier paroxysmal symptoms typical of thrombo-angiitis obliterans affecting the cerebral vessels, points the probability that the mental symptoms were likewise due to the vascular condition. A difficulty in attributing the mental symptoms to the same vascular condition in the brain as the other cerebral symptoms mentioned above is that whereas the latter were paroxysmal and transient the former were long-sustained.

There are two distinct physio-pathological mechanisms at work in thrombo-angiitis obliterans: one a slow and progressive occlusion of the vessel or vessels affected, and the other a paroxysmal functional disturbance induced by the physical changes in the vessel wall. In time, as Scheinker and others believe, the recurrence or the prolongation of the functional disturbances leads to its irreversibility. It may, however, be that the progress of the organic change in the vessel wall produces a parallel and permanent alteration in the functional capacity of the vessel wall. For a greater or lesser period it is possible to distinguish the effects of the two mechanisms—the spasmodic physiological disturbance and the progressive pathological lesion. In the legs, for instance, intermittent claudication not infrequently occurs in association with advancing early gangrene. It can be assumed that the same thing happens in the brain, the temporary physiological disturbance producing transient symptoms, the permanent organic change enduring symptoms.

The paroxysmal character of some of the symptoms found in thrombo-angiitis obliterans may possibly be accounted for by partial occlusion of a vessel from temporary spasm, or by temporarily complete occlusion from organic change in the vessel wall plus passing spasm. As for the enduring symptoms present they result, of course, from the irreversible occlusion of a vessel, most probably from the combination of organic change in the vessel and permanent loss of functional capacity. Even the enduring symptoms,

it should be noted, do not necessarily advance consistently and continuously: the establishment of collateral circulation, for instance, may arrest or slow their progress.

How is the presence of mental symptoms in a case of thrombo-angiitis to be explained, presuming that the concurrence is connected and not accidental? Mental symptoms, as we know, may occur in the absence of any demonstrable pathological condition in the brain; and it is still possible that mental symptoms may occur in the presence of thrombo-angiitis obliterans of brain vessels without any parallelism between the two. The physical event may have set the condition alight, though not in the direct way that a spasm or occlusion of a vessel produces a symptom, and there their relationship ends. If the mental symptoms should indicate permanent intellectual loss such as occurs with organic brain change, there will be no difficulty in attributing them to destruction of brain tissue from occlusion of the supplying vessel. In addition to the guidance derivable from the nature of the symptoms present their duration gives some indication of their genesis. If the mental symptoms are as fleeting as, say, neurological symptoms occurring in the course of thrombo-angiitis of the cerebral vessels may be, then there need be little hesitation in attributing them to the temporary vascular disturbance that is characteristic of the earlier stages of thrombo-angiitis. The difficulty arises with the more protracted psychotic episodes. I think the explanation here is, working on the assumption that there has been a thrombo-angiitic attack upon one or more of the cerebral vessels, that this event has acted as a trigger stimulus provoking a psychosis. It was this mechanism that produced the psychosis in the case described in this paper. The patient was, moreover, already predisposed to the occurrence of such an event through the action of heredity and recent mental stress. It is just possible that prior to the removal from medical care the patient was beginning to evince evidence of intellectual dissolution—he did not continue long enough under observation for this impression to be confirmed—and if this should be so an organic change was then overtaking symptoms produced by the mechanism described above.

There can be little doubt that the toe condition for which the patient first came under observation was already the beginning of the thrombo-angiitis—though he attributed it to an injury—and the recurrent cardiovascular collapses, though they took place after periods of acute excitement, were probably occasioned by spasm of the coronary arteries associated with early thrombo-angiitis. It is possible that the physical effects of the prolonged excitement may have prepared the ground for such an event. There may also have been involvement of the mesenteric vessels, when the patient passed blood in the stools. If these views are correct the case described has presented the features of thrombo-angiitis occurring in the vessels of the legs, brain, heart and mesentery, which, judging by the literature, are the more common sites of election of the condition.

Summary.

A case is described in which mental symptoms, predominantly manic, epileptiform fits and several other cerebral symptoms—diplopia, dysarthria—

have occurred in association with gangrene of the feet due to thrombo-angiitis obliterans, and considered to be due to the same vascular condition. Allusion is made to some views of the pathology of the condition, and the manner in which it affects the functional capacity of the blood vessels.

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MEPACRINE PSYCHOSIS.

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From time to time in the Middle East, cases were admitted into hospital bearing the diagnosis of Mepacrine Psychosis. This was a label which one hesitated to accept because, for one thing, the cases presented no single clinical type, and for another, they showed, with few exceptions, little or no evidence of symptoms of an organic reaction type such as might be expected in a toxic psychosis. It was, moreover, important, in view of the widespread use of mepacrine both as prophylactic against malaria and in the treatment of it, that the occurrence of a psychosis during the exhibition of mepacrine should not be ascribed to it, except on the irrefutable evidence of a causal connection between the two. Though I have no figures to indicate the incidence of mepacrine psychosis relative to the number of cases of malaria treated with the drug in the M.E.F., I believe the ratio to be very small indeed. Kingsbury mentions 12 cases among several thousand cases of malaria treated with mepacrine ; Allen *et al.* quote Greene as having encountered 2 cases in a series of 750 so treated, in Malay. Hoops had 1 case of mental excitement among 1,207 cases ; Briercliffe 15 cases of delirium among some hundred persons taking mepacrine. Field estimated the incidence of mepacrine psychosis to be less than 0·1 per cent. of cases treated. Gaskill and Fitz-Hugh noted 35 cases of toxic psychosis in 7,064 cases of malaria treated with mepacrine in an army hospital during the recent war ; Mergener reports 1 case in 1,000, and quotes Udalagama, who recorded 7 such cases in a series of 644, and Bispham, who noted only 1 case in 7,915 cases that came under his personal supervision, and who up to 1941 found only 35 instances in the literature. Burnham quotes Dove as having noted no case of alarming reactions (presumably including psychotic reaction) in a series of 30,000 cases treated with mepacrine.

The present review is based on 33 cases, 25 of which I had myself had the opportunity of seeing during their stay in hospital. It was possible to determine in 10 of the cases that the psychotic symptoms had commenced prior to the exhibition of mepacrine, and had been precipitated either by the malaria or by circumstances antecedent to it. In 7 of these cases the symptoms were aggravated by the mepacrine, and in 3 it had no influence. It is possible, therefore, to divide the cases into 3 groups : those in which psychotic symptoms followed the exhibition of mepacrine and which can, therefore, be legitimately

regarded as having been precipitated by it, designated group A ; those aggravated by mepacrine, designated group B ; and those that appear to have been precipitated by the malaria, designated group C. Groups B and C have cases in common, which fall to be included in each of the groups. The number of cases in each of these groups is, 23 in group A, 7 in group B, and 8 in group C. This division permits of the rejection in the study of mepacrine psychosis of groups B and C, and of their utilization for the purpose of making comparisons between the groups in several particulars. All the observations that follow relate to group A, therefore, unless otherwise specified.

Cases Precipitated by Mepacrine : Aetiology.

All 23 cases are of the male sex, and all British except for 2 Palestine Jews. The average age is 28 ; the extremes of age are 20 and 44 ; and 87 per cent. of the cases fall into the 20 to 35 age-group. The proportion of officers and N.C.O.s to privates and equivalents (11 to 12) is high compared to their ratio in the services. The intelligence levels of the cases, though the records are incomplete in this respect, point, as far as they go, to a scatter not differing from that found in the Services generally. The types of psychological make-up found in the series show perhaps an unduly high proportion of the schizoid type, and evoke the suggestion that the schizoid personality may possibly be more susceptible to mepacrine than the other types. But the immunity shown by the many schizoid individuals who have taken mepacrine without ill-effect and the occurrence of mepacrine psychosis in other than the schizoid types indicate that susceptibility to mepacrine does not reside exclusively in the mental and emotional constitutions of the individuals affected. The distribution of the various types was as follows : Schizoid type 27 per cent. ; obsessive, anxious and immature types, each 13 per cent. ; an assortment of cyclothymic, psychopathic and hysteroid types 21 per cent., and unclassified 13 per cent.

As with most psychiatric breakdowns, the aetiology of the mepacrine-precipitated cases reveals a multi-factorial origin. In addition to the toxic effect of the malaria, which can be presumed to have been an active contributory factor in all the cases, the following other factors are recorded in more than half the cases (13) :

Emotional stress (other than that of battle)	7 cases.
Recent battle stress	3 ,,
Alcoholism	2 ,,
Infective hepatitis	1 case.
Sundry factors (P.U.O., septic process, ? cholecystitis)	3 cases.

A noteworthy feature of the cases in the series is that 11 of them (47·8 per cent.) give a history of one or more attacks of malaria in the 18 months prior to the psychiatric episode, and 2, malarial attacks prior to that. Gaskill and Fitz-Hugh have recorded that most of the 35 cases reviewed by them had had one or more attacks of malaria in the past. A constitutional pre-disposition to psychotic breakdown is evident in only 3 of the present series, these having

had previous psychotic breakdowns, whilst the third had a further attack of mania 14 months after the mepacrine-precipitated attack. Three cases give a family history of psychopathy or insanity. Kingsbury noted that one mild and one severe case, in his series of 17, gave histories of previous mental breakdowns. Four of the 9 cases reviewed by Allen *et al.* had had previous " nervous or mental symptoms," and 6 had associated physical conditions which could have been predisposing factors.

Gaskill and Fitz-Hugh found infection with *P. falciparum* to be twice as frequent as infection with *P. vivax*, but this applied equally to the 7,064 cases of malaria as to the 35 cases that developed toxic psychosis. They found no evidence of mental instability in their cases, and suggested vitamin deficiency as a possible contributory cause.

Idiosyncrasy.

No evidence of idiosyncrasy to mepacrine is forthcoming in the author's series. It is inconstant in its toxic effect. Fourteen cases had had mepacrine with impunity in the 18 months prior to their breakdown, and 3 subsequent to it. In only one case did psychotic symptoms reappear with the treatment of malaria, and in that case mepacrine was not exhibited : quinine and plasmoquine were employed. Gaskill and Fitz-Hugh noted that 16 of their recovered cases were at a later date retreated with mepacrine, 15 without any manifestation of untoward symptoms. Shiers reports a case which does, however, suggest that idiosyncrasy for mepacrine may exist. During a period of 10 months his patient had taken mepacrine on 3 occasions in different daily and total dosages, and developed mental symptoms on each occasion.

Dosage and Toxicity.

The dosage of mepacrine used undoubtedly has some influence. In only one instance in the present series did the prophylactic dose (1–2 tablets daily, equal to 0·1–0·2 g.) produce psychotic reaction. The patient was employed in a highly malarious area and had been taking 2 tablets daily for 9 months when symptoms appeared. The breaking-off of the engagement by his fiancée probably played a contributory part. He recovered following convulsive treatment (6 convulsions), but no sooner had that happened than he had a malarial relapse, was given mepacrine and promptly reacted with psychotic symptoms again. With cessation of the mepacrine and two convulsions he was once more restored to normality. Kingsbury records the occurrence of mepacrine psychosis after a dosage as low as 0·6 g. The medical consultants of the United States Army, without adducing supporting figures, give their opinion that psychological disturbances in association with mepacrine are mostly due to " unduly large doses," and note that they have also occurred in connection with suppressive medication. Burnham, on the other hand, records a case of attempted suicide with mepacrine, in which 90 gr. were probably ingested, though an undetermined amount was rejected in the vomit, and though the patient became unconscious and stuporose within 6–7 hours, he regained full consciousness within 48 hours with no development of psychotic

symptoms. Greene's 2 cases developed psychotic symptoms at the end of 6 and 7 days respectively after taking 3 daily tablets (0·3 g.). The case described by Shiers first developed mental symptoms following suppressive mepacrine, 0·1 g. daily, and subsequently during the treatment of malaria, with a daily dose of 0·6 g.

The relation of mepacrine dosage to body weight has been offered as explanation for its toxic effect. In the present series 4 cases are recorded as underweight and of poor physique.

Kingsbury ascribes the toxic effect of mepacrine to two factors, one, to the liberation of toxins by the action of the drug on the malarial parasite, and the other, to the toxic effect of mepacrine on the C.N.S. Turner considered the effect to be due to drug idiosyncrasy, pointing out that the amount of mepacrine taken was not sufficient to produce the symptoms usually associated with the toxic effects of the drug. The study made by two interns, quoted by Allen *et al.*, who gave 1½ gr. mepacrine 3 times daily for 5 days to 2 normal male subjects, who showed no signs of malaria, suggests, however, that mepacrine is toxic in therapeutic doses. Both cases felt exhilaration on the fifth day, one also noted insomnia, and one, at the end of the course, showed flight of ideas, distractibility and a constant stream of irrelevant talk. The factor of suggestibility could not be ruled out in either case. They incline to think that the delayed excretion of mepacrine, for one reason or another, may account for its toxic effect.

The factors that probably act adjuvantly to mepacrine and render it toxic in medicinal doses are: the total amount taken relative to body weight; bodily conditions delaying its excretion, such as constipation, hepatic and renal diseases, disturbed water balance; idiosyncrasy to the drug in rare instances; predisposition to mental breakdown, inherited and acquired; intercurrent stress, physical (infection, especially), emotional and mental. It is necessary in addition to postulate the existence of an individual factor of transient nature to explain the inconstant effect of mepacrine where such factors as have been mentioned above have remained constant, as far as can be judged, but where the mepacrine has induced a psychotic reaction on one occasion and not the next. Investigation of the mepacrine blood level in relation to the onset of mental symptoms may yield useful information, but so far none is available in the literature.

Time of Onset of Symptoms.

About the middle of 1944 the dosage of mepacrine used in the treatment of malaria in the Middle East for cases arriving from Italy and Sicily was standardized at 3·4 g., given over 6 days, followed by maintenance doses of 0·1 g. daily for at least a month. This became the standard treatment for British and other European troops in 1945. Prior to 1944 the standard Q.A.P. treatment of malaria was used, entailing a dosage of mepacrine of 1·5 g. given over 5 days. Where psychotic symptoms developed they occurred during the course of the intensive mepacrine treatment, usually on the third or fourth day (33 per cent.), or at various times following it, mostly within a

week of termination of intensive treatment (67 per cent.). In only one case did symptoms appear before the third day. Twenty-one days following intensive mepacrine dosage was the latest at which it seemed reasonable to connect the symptoms with the mepacrine. One case was, however, admitted to hospital considerably later (3 months), the symptoms having developed relatively slowly to the point where behaviour was affected ;* Kingsbury noted the minimum interval between the commencement of treatment and the onset of symptoms to be 1½ days, and the maximum 12 days (5 days after the completion of the course), with an average of 5½ days ; the 9 cases reviewed by Allen *et al.* averaged 6·5 days, the dosage used was 1·5 g. given over 5 days. The dosage given in the series of 35 cases reviewed by Gaskill and Fitz-Hugh was 2·1 g., and the onset of psychotic symptoms ranged from the third day of treatment after 0·9 g. of mepacrine had been taken, to 12 days after the completion of treatment. The most frequent was 6 days after completion of treatment. They note in addition, that the onset was often insidious. Field observes that mental symptoms commence just before or just after the end of treatment. Mergener's case developed mental symptoms on the fifth day, after having taken 2·8 g. mepacrine.

It would appear that the later symptoms become manifest the less favourable is the early progress of the case. As Table I indicates, the cases in which symptoms commenced during the period of intensive mepacrine intake (group A) give a ratio of 1 to 1·5 between those recovering within 2 months and those not recovering within this period, whilst in group B, in which symptoms appeared after the completion of the intensive mepacrine course, the ratio is 1 to 3. The difference, however, is not significant, χ^2 being 1·8 and p 0·15 approximately.

TABLE I.

	Recovered within 2 months.	Not recovered within 2 months.
(*a*) Symptoms commencing during period of intensive mepacrine dosage .	4	6
(*b*) Symptoms commencing after completion of intensive mepacrine dosage .	5	15

SYMPTOMS.

The types of reactive condition induced by mepacrine may be gathered from Table II.

The two most frequent are the schizophrenic and manic reactive ones. In several cases it was impracticable to designate the reaction as either simply manic or schizophrenic, for they showed features of both types of reaction, an exaltation of psychomotor activity and mood coupled with schizophrenic type of ideation ; and the reactions were accordingly designated as manic-schizophrenic in type. One observation stands out clearly, namely, that mepacrine tends to produce a manic rather than a depressive setting. Thus in Table II, though the figures are too small for valid statistical deductions,

* and is included among the mepacrine-precipitated cases.

TABLE II.—*To Show Reaction Types and Main Features of Cases.*

	Group A. (Precipitated by mepacrine.)		Group C. (Precipitated by malaria.)		Group B. (Aggravated by mepacrine.)	
	No.	%.	No.	%.	No.	%.
Schizophrenic reaction	8	34·8	3	37·5	4	57·1
Manic reection	4	17·4	1	12·5	..	
Manic-schizophrenic reaction	4	17·4	..		..	
Depressive reaction	3	13	2	25·0	2	28·6
Confusional reaction	1	4·35	..		..	
Alternating manic and depressive phases	1	4·35	1	12·5	..	
Personality change, ? schizophrenic	1	4·35	..		..	
Behaviour disturbance	1	4·35	..		..	
Paranoid reaction	..		1	12·5	1	14·3
Totals	23	100·00	8	100·0	7	100·0
		% of 23.		% of 8.		% of 7.
Showing schizophrenic features	12	52·2	3	37·5	4	57·1
,, manic ,,	9	39·1	2	25·0	..	
,, depressive ,,	4	17·4	3	37·5	2	28·6
,, confusion ,,	3	13	..		..	
,, personality change	1	4·35	..		..	
,, behaviour disturbance	1	4·35	..		..	
,, paranoid reaction	..		1	12·5	1	14·3

it is seen that mepacrine produces manic and depressive features in the ratio 9 to 4, whilst malaria yields a ratio of 2 to 3. Carrol C. Turner refers to Forrester's experience with the British Salonica Force, 1918–19, that, after mental confusion, depression was the earliest and most prominent symptom found in association with malaria. With mepacrine, as the present series indicates, and as is confirmed by the literature on the subject, the mood change produced is one of elation and euphoria frequently leading to acute mania. A simple confusional picture was present in only one case, though transient and mild confusional symptoms were noted in 2 cases of mania. If there is any one type of reaction that is characteristic of mepacrine psychosis it is the manic-schizophrenic syndrome mentioned above. Though it occurs in distinctive degree in comparatively few of the cases (4 or 17·4 per cent.), it does not appear in group C (precipitated by malaria). Some of the cases diagnosed as schizophrenic exhibited manic features in the early phases, but because they were neither prominent nor persistent they were not labelled manic-schizophrenic. Similarly, several of the cases diagnosed as manic, when fully developed, showed schizophrenic features. These cases reinforce the impression of the peculiar effect of mepacrine in inducing an exaltation of mood coupled with a schizophrenic type of thought disturbance. If the 3

types of reaction manifesting manic and schizophrenic features at one or other time in their course, namely, the manic, schizophrenic and manic-schizophrenic reactions, are grouped together, the incidence of the syndrome comprising the features mentioned is about 70 per cent. It is higher still, 78 per cent., if the 2 cases noted further, which commenced as a manic reaction and personality change respectively and developed later into schizophrenic states, are added.

The onset of psychotic symptoms is signalized by insomnia almost invariably, and in the non-depressive cases by a sudden change of behaviour, with usually an outburst of noisy talkative excitement. The psychotic picture develops rapidly thereafter. There is a brief phase lasting a day or two, characterized by features such as puzzlement, fleeting ideas of influence, a loss of personality and reality sense, a degree of emotionality and, in some cases, transient confusion and disorientation. The mood then changes to the more characteristic and enduring one of elation and euphoria. With this the thought content becomes delusional and the behaviour disordered, sometimes grossly. The delusions are of an exalted character relating mostly to the patient's social position and work. The patient soon begins to interpret his experiences—the loss of inhibition and the elation—in a spiritual, religious light, and this is followed by failure of co-ordination of thought and the expression of bizarre ideas such as are commonly present in typical cases of schizophrenia. The delusional trend of thought is not maintained long enough for the delusions to acquire any degree of systematization. Insight is totally lost only for the brief period of the climax which the development of symptoms quickly reaches; it is present both before and afterwards, if often only fleetingly. When within a few weeks or months improvement commences, it proceeds rapidly to full recovery. In the cases that do not progress to recovery, evidence of dementia quickly supervenes on the acute stage of florid symptoms; there is deterioration of the personality, the manner becomes facile, and affect and interest are dulled.

Turner remarks on the maniacal nature of the reaction to mepacrine; he observes that the condition merges into a "somnolent delirium" or even "deep coma", but this was noted in only 2 cases in the present series, and in both there was a complicating factor that may have accounted for the unusual type of reaction. One case had had infective hepatitis coincidentally with the malaria. Fourteen days after discharge to convalescence the patient became sleepless, restless, noisy, loquacious and aggressive, and was admitted to the psychiatric hospital (78th) in this condition. E.C.T. (twice) and sedation had little effect, and 10 days after admission the patient lapsed into a comatose state, with acetone in the breath and urine and raised temperature (up to 101°). The other case had been treated with mepacrine, though malarial parasites had not been found in the blood. It had, in fact, been labelled as P.U.O., and whatever the nature of the infective agent may have been it appears to have invaded the central nervous system, for the C.S.F. was found to be slightly turbid and the cells increased to 12 per c.mm. No organisms were found. Urine culture was negative, and blood agglutination for typhus, typhoid and *Brucella* not abnormal. The blood showed a leucocytosis with

a count of 12,300 (P. 51%, L. 47%, M. 2%). On the third day of mepacrine treatment the patient developed maniacal symptoms, his physical condition deteriorated with the excitement, and he slipped into a muttering delirium 6 days later.

The two cases seen by Greene, as quoted by Allen *et al.*, are described as cases of "cerebral excitation"—they were hilarious and excited, danced and sang. The 9 cases they review give the following distribution of reactions: excitement, closely resembling mania, 5; mild excitement with confusion, 2; almost no excitement but severe confusion, 2. Gaskill and Fitz-Hugh also note the two types of condition; the one showing increased motor and psychomotor activity, euphoria and expansiveness, auditory and visual hallucinations and delusions, and occasionally disorientation; the other, with insidious onset, showing gradual clouding of the sensorium, disorientation and loss of recent memory and diminished motor and intellectual activity. "The latter patients were withdrawn and seclusive, the affect being one of bewilderment and fearfulness." Udalagma, quoted by Mergener, notes that amnesia follows the acute symptoms of excitement, confusion and disorientation. Mergener's case manifested an initial manic phase followed by a depressive one on the third day in a confusional setting. With improvement, an extensive amnesia was noted. The patient described by Shiers developed exaltation of faculties on each of the three occasions that he took mepacrine.

When psychotic symptoms have preceded the exhibition of mepacrine, their aggravation by it is less dramatic in onset, but is none the less clearly recognizable. The change produced is one of degree and not of kind.

Clinical Pictures.

The clinical pictures presented by the various types of reaction may be better appreciated from the description of a few representative cases:

F. H. B—; aged 36; Flying Officer; bank clerk in civil life; maternal uncle insane, aunt alcoholic; schizophrenic reaction type.

Admitted to hospital for B.T. malaria and placed on mepacrine. Following day suddenly began declaiming to the ward: "The world does not exist, never has and never will. Ladies and Gentlemen, this is the end of the world. I am going to die. For Jesus Christ's sake, kill me," etc. Next day, in more tranquil and clearer state of mind, clearly recalled what he had been saying, explaining that he felt as if the words were being put into his mouth, thought he was going to be killed and felt muzzy. After a fortnight, presumably having shown no further outward symptoms of mental disturbance, he was discharged, but his behaviour became rapidly abnormal again, so that he presented himself at a R.A.F. station completely naked, having walked there in this state some 500 yards from his hotel, and was readmitted to hospital. He reported that he was under the compulsion to find out what was wrong with the world, so as to put it right, that he did not know how he was going to do this, but that as a preliminary he thought he should have his head and legs cut off. His talk was rambling and showed flight of ideas. A week later there was less psychomotor excitement: his manner was, however, facile, and he frequently affected an inane smile. He displayed neither insight nor concern about his circumstances or his future. Occasional thought-blocking was observed. Still referred, but without any display of emotion, to being responsible for the evil in the world. Two months later he was recorded as recovered.

J. J. G—; aged 30; Sergeant, Regular; married; manic reaction type.
Had two attacks of malaria and two complete courses of mepacrine therapy, over a period of 3 months. At the end of the last course became sleepless and restless and his manner changed: was argumentative and paranoidal in outlook. On admission he was talkative, overactive, euphoric and exalted; declared there was nothing wrong with him, and smiled inanely and was generally facile; claimed to have a scheme for repaying the National Debt and asked to see the O.C. hospital regarding it. He recovered rapidly within 3 weeks of admission.

W. H—; aged 31; Regular Officer; manic-schizophrenic reaction type.
Seen when he had more or less recovered from the acute symptoms a fortnight after their commencement, he gave the following account of their development. On completion of mepacrine course and on the eve of his discharge from hospital, he began to experience acceleration and press of thought and a feeling of excitement. Next morning, returning to unit, felt he was talking brilliantly and more than was his wont. Then quickly followed a feeling of light-headedness and puzzlement and disordered thought and behaviour. His talk became rambling and disjointed. Had idea that he was being watched and that he was being influenced in his actions, and resisted this. In recall, says of this period, he felt as if in a trance, only hazily appreciating his surroundings and his actions, and that on admission to hospital he felt worried by changes he noted since he was previously there (2 days ago). Thought he had been dead for a year, and that he had resuscitated himself through will-power. "If I wished I could be God, but preferred to remain on earth. I could live for ever. I felt I was a saint and dead, turned to dust, a speck on top of the pyramid. I could get right within myself outside space. My body was indestructible. I had split the atom and feared I might blow up the whole earth. Black and white had met, I had won a colossal sweepstake and was the Supreme Being. I thought I was the genius who was running the war, and that Churchill, Roosevelt and Stalin had met to consult me." Conceived the idea that he was Prince John (who was born same year as himself), and that he was being used as a "whispering gallery for deception." "I have had ups and downs whilst here. In my ups I think I am God, marvellous at everything; in my downs worry whether I am a degenerate, whether I have infantile palsy and worry about my recent experiences." On admission to hospital, he looked vacant and bewildered, addressed the M.O. casually, asking, "Who am I, what am I?" He was not, however, disorientated, and his memory was unimpaired. His manner was grandiose: mood, one of elation. He was talkative, wrote many disjointed letters, and drew up scribbled plans for finishing the war, for demobilization, etc. Expressed numerous delusions of exaltation—that he belonged to Royalty, was to receive the V.C., get high promotion, etc., and showed such poor sense of reality that he was frequently bidding the staff farewell as he was about to set off in execution of his ideas. At one time or another he mistook identities and manifested depersonalization and feelings of passivity. He frequently passed irrelevant remarks, was hallucinated, especially at nights. At times noisy and overactive. He was, however, possessed of a degree of insight, and was not altogether detached from reality; though he behaved at times as if he were unable to distinguish between fantasy and reality.
He had only one testicle; the other had atrophied he said, following a kick at 17. He was unmarried and was a latent homosexual with strong though repressed homosexual urges. Had guilt feelings regarding masturbation. Had never had intercourse. Was a hard-working and very conscientious officer, and had gained the M.C. at Dunkirk.

R. C. E—; aged 31; Private; manic-schizophrenic reaction type.
In the night following completion of course of mepacrine for M.T. malaria became restless and rowdy, talked irrationally. On admission to hospital was disorientated as to place and person, showed psychomotor over-activity and mild flight of ideas. Slightly elated, and later euphoric, expressed a number of bizarre delusions—his thoughts were being read, he was a Brigadier, had put an end to the war—but he had fleeting insight. The psychiatrist in charge expressed the view that the case had never appeared as a true toxic confusional picture, and considered it a schizophrenic episode. Five months later he was declared recovered.

B. N—; aged 24; Private; single; manic-schizophrenic reaction type.
Whilst having mepacrine treatment for malaria became elated and excited; declared he had received the gift of the Holy Spirit, felt raised above worldly things and believed he would never be able to procreate. He wrote to the Under Secretary of State for War outlining a scheme for establishing a training college for social and religious workers. "I have the greatest message for the world in 2,000 years," he wrote, "I shall never sleep again in this life for the simple reason that it would be totally unnecessary. I am Christ reborn." At times grinning and mumbling to himself. Despite his delusions, his behaviour was correct. Recovered within fortnight of onset of symptoms. Though S.G. 1, had failed twice in his matriculation examination prior to the war; had fallen in love with his crammer's wife. Had recently started studying for it again in off-duty hours.

G. B—; aged 37; Lieutenant; married; depressive reaction type.
Father committed suicide at 44; mother had mental illness prior to death at 55. Trained as solicitor, but not feeling fit to practice took up teaching. History of mood swings. Whilst undergoing mepacrine treatment for M.T. malaria developed mental symptoms, depression without retardation, marked ideas of unworthiness, ideas of reference. Demanded to be sent back to unit to stand trial for desertion, believing his army career to have been a succession of failures. "My name must be mud all over the Arakan. They are talking of throwing me into the water as a fifth columnist." His *rapport* was good and there was no disharmony of mood and thought. Had a slight stammer, tachycardia, exaggerated reflexes.

H. C—; aged 31; Sergeant, Regular; single; confusional reaction.
Had 5 attacks of malaria in the past 2 years. A month ago broke off his engagement. With present malarial relapse was placed on mepacrine and on third day his speech became slow and incoherent, his mood oscillated between elation and depression, vomited after food and was incontinent. Twelve days later his answers were monosyllabic and absurd; he was slow in carrying out physical movements to order and was still incontinent. Physical examination and investigation of blood and C.S.F. were negative. By the time of his admission to hospital, 3 weeks after commencement of symptoms, the mental state had cleared and he rapidly regained normality.

J. W. W—; aged 31; C.S.M., Regular; single; instance of aggravation of pre-existing symptoms by mepacrine.
Returned home after 8 years' service abroad. Had difficulty in accommodating himself to the changed circumstances of life. In his absence overseas, mother and brother had died, and on returning felt alone in the world. Also felt he could not measure up to the job of instructor which he was given. Developed a mild reactive depression, and was recommended for admission to a neurosis centre. Whilst waiting to enter the centre he had a malarial relapse, was admitted to hospital and placed on mepacrine. Insomnia and depression increased, feared he was going insane, and in a state of utter misery, 3 days after commencing mepacrine treatment, made suicidal attempt by cutting wrist. The acute depressive symptoms cleared quickly, but anxiety symptoms persisted for more than 6 months.

Prognosis.

Fourteen of the 23 cases (68 per cent.) recovered within 6 months of onset of symptoms; 1 in 14 days, 4 in 22 to 25 days, 4 in 2 months, 2 in 3 months, 2 in 7 months, 1 in 5 months. The average was 62 days. In Table III the development reached at the end of 2 months is shown. The cases are divided between the manic and schizophrenic sub-group and the remainder. The figures point to an earlier recovery for the manic and schizophrenic sub-group than for the other cases in the group: the ratio of recovered to non-recovered is 7 : 9 for the former and 2 : 5 for the latter. The difference, though suggestive,

is not significant. What the recovery rate would be had it been possible to follow up all the cases to, say, 6 months, it is difficult to say, but of the 15 cases followed up for that period, 14 recovered.

TABLE III.

	Manic and schizophrenic sub-group.		Remaining cases.		Total.	
	No.	%.	No.	%.	No.	%.
Recovered* within 2 months	7	43·8	2	28·6	9	39·1
Not recovered† at end of 2 months	9	56·2	5	71·4	14	60·9
Totals	16	100·0	7	100·0	23	100·0

* Included improved.
† Including improved followed by relapse.

No appreciable difference in the tendency to early recovery between the various clinical types included in the manic and schizophrenic sub-group is detectable (see Table IV).

TABLE IV.

	Schizophrenic type. No.	Manic type. No.	Manic-schizophrenic type. No.
Recovered within 2 months	3	2	2
Not recovered at end of 2 months	3	1	..
Total	6	3	2

Greene's cases, quoted by Allen *et al.*, recovered within 24 to 48 hours. The 9 cases reviewed by them give an average duration of symptoms of 15·1 days. The symptoms in Field's case lasted approximately 1 week. Thirty-three of the 35 in the Gaskill and Fitz-Hugh series recovered within a range of 8 to 85 days, with an average of 23 days. In the 2 patients who failed to recover, they considered a schizophrenic reaction had been precipitated. Five of Udalagama's 7 cases recovered in from 17 hours to 41 days, one died of exhaustion and other complications, and one developed chronic mental symptoms. Bispham's case recovered in 22 days, Mergener's in 14 days.

The stages reached at the end of 2 months by the non-recovered cases in the author's series were as follows :

(*a*) Schizophrenic reaction type :
  (i) Showing further deterioration 1
  (ii) Showing relief of acute symptoms but with residual dilapidation 2
(*b*) Manic reaction type :
  Showing schizophrenic development . . . 1
(*c*) Manic-schizophrenic reaction type :
  Showing dilapidation and instability . . . 1

(*d*) Depressive reaction type :
(i) Showing schizophrenic development . . 1
(ii) Unchanged 2
(*e*) Personality change—? schizophrenic development . 1

It will be observed that in addition to the immediate manic and schizophrenic reactions to mepacrine, 2 cases, commencing in other guises, developed schizophrenic symptoms.

Age-Incidence.

A comparison between cases precipitated by mepacrine and those precipitated by malaria suggests that mepacrine psychosis is more likely to occur in the older than the younger soldier. This may be connected with the observation previously made, that there is a relative preponderance of officers and N.C.O.s amongst the cases of mepacrine psychosis reviewed. In the 20–25 age-group the ratio of officers and N.C.O.s to private and equivalent ranks is 2 : 7, whilst above 25 the ratio is 4 : 3. Table V indicates a ratio of approximately 2 : 3 for the incidence of mepacrine psychosis in the age-groups below and above 25, whilst with psychosis precipitated by malaria it is the reverse—5 : 3. The difference is not, however, statistically significant.

Table V.

Age-period.	Group A. (Pptd. by mepacrine.)				Group C. (Pptd. by malaria.)			
	No.	%	No.	%	No.	%	No.	%
20–25	9	39·1			5	62·5		
26–35	11	47·8	14	60·9	1	12·5	3	37·5
36–44	3	13·1			2	25·0		

The reaction is more likely to be schizophrenic in type in the younger age-group, 20–25 ; the other reactions mostly occurring in the older age-groups, 26 and above. This may be gathered from Table VI.

Table VI.

Age-period.	Schizophrenic reaction.		Other reactions.	
	No.	%	No.	%
20–25	6	75·0	3	20·0
26 and over	2	25·0	12	80·0
Totals	8	100·0	15	100·0

There does not appear to be any notable connection between personality make-up and the type of psychotic symptoms precipitated by mepacrine. Two of the 3 depressed cases gave a positive family history of psychopathy or insanity, whilst in the manic and schizophrenic sub-group a positive history occurred in 2 of the 16 cases. Emotional stress, other than that of battle, figures as a contributory factor in 4 of the 8 cases of schizophrenic reaction type, as against its occurrence in 3 of the 15 other cases. It is, perhaps, noteworthy that the schizophrenic reaction type is not associated with any history

of earlier breakdowns. There are no significant differences in the previous incidence of malaria amongst the different types of reaction.

Mepacrine staining was noted in 7 cases of group A (30·4 per cent.) and in 3 cases in group B (42·9 per cent.). It was more or less proportionally distributed among the various reaction types. Eight of the 9 cases of Allen *et al.* developed pigmentation. Mepacrine pigmentation is said (Manson) not to occur before the third day, and probably it is not without significance that mental symptoms likewise appear from the third day on, as a rule. The intensity and duration of the staining are affected by intercurrent infections and factors interfering with the elimination of mepacrine, as, e.g., constipation. It may persist as long as 3 months (Manson). The elimination of mepacrine from the body is slow, and may not be completed for as long as a month. The rate of elimination probably influences the duration of symptoms resulting from the mepacrine.

Effect of Convulsive Treatment.

Four cases in group A and 2 in group C received electrical convulsive treatment. Cessation of mepacrine will, no doubt, have played a part in determining such favourable results as were obtained, but the symptoms did not promptly disappear with the stoppage of mepacrine, and the beneficial influence of the convulsive treatment cannot be denied. Four (2 cases of schizophrenia and 2 of depression) of the 6 cases showed improvement and remission against 2 unchanged. Two (one case of schizophrenia and one of depression), however, relapsed shortly after treatment. The number of convulsions given ranged from 2 to 6, averaging 4·6.

Combining such figures cited in the literature, as are relevant, with those of the writer's series provides the following data : The incidence of mepacrine psychosis amongst the cases of malaria treated with mepacrine is 0·25 per cent. (47 in 18,580) ; the minimum dose of mepacrine which has induced psychotic symptoms has been 0·45 g., and the symptoms have appeared as soon as 1½ days after the exhibition of mepacrine and as late as 21 days. The recovery-rate has been 81·4 per cent. (57 cases out of 70). The duration of symptoms has ranged from half-a-day to 5 months ; with an average, for the 51 cases having the averages recorded, of 32 days. 10 per cent. approximately of the cases give a history of previous mental breakdown (8 in 81 cases), and 11·6 per cent. a positive family history (5 in 43).

Differential Diagnosis.

The differential diagnosis of mepacrine psychosis presents two problems : one, the differentiation from cerebral malaria and, two, from an endogenous or biogenic psychosis. The mental symptoms of cerebral malaria, as usually manifested, come on more precipitately and are more acute in nature. In association with hyperpyrexia the patient develops delirious mania or muttering delirium, rapidly becomes unconscious and comatose ; or without hyperpyrexia, coma or epileptiform convulsions suddenly develop, preceded perhaps in some cases by such premonitory symptoms as severe headache, drowsiness,

irritability, muscular twitchings. Difficulty of differential diagnosis is only likely to arise in those uncommon instances where mepacrine induces delirium or coma. Similarly, difficulty will be experienced in the presence of the less common and less dramatic forms of cerebral malaria, which may simulate almost any type of mental disorder. The course and severity of the malarial attack and the patient's physical condition may point to the presence of cerebral malaria, whilst the time-relationship of onset of symptoms with the exhibition of mepacrine, and possibly also the improvement of symptoms on ceasing mepacrine, will indicate the presence of mepacrine psychosis. In the cerebral forms, malarial parasites are usually scanty in the peripheral blood. The differentiation from a biogenic psychosis is a more difficult problem, because mepacrine does sometimes precipitate a condition indistinguishable from a biogenic psychosis. If recovery within 2 to 6 months may be taken as presumptive evidence in favour of regarding such cases as those of an acute reaction to mepacrine, there remain 9 of the 23 cases precipitated by mepacrine, which not having recovered at the end of 2 months, become suspect cases of biogenic psychosis. It is likely, of course, as has already been pointed out, that some of these cases, had it been possible to follow them up for, say, 6 months, might have shown recovery. However, reckoning with the possibility that these 9 cases may be instances of biogenic psychosis, we find, on analysing the stages of development reached by them at the end of 2 months, that 2 had developed into schizophrenia, 1 looked very much like a schizophrenia, 3 showed mental deterioration and 3 improvement of the florid symptoms, but with residual dilapidation of the personality. It will be seen, therefore, that at least 5 of the cases, namely, those showing either schizophrenic development or mental deterioration, suggest the presence of a biogenic psychosis. The series of 23 cases divides itself, therefore, into 18 of acute reaction (78·3 per cent.) and 5 of possible biogenic psychosis (21·7 per cent.). It may, of course, be that the biogenic psychosis is to be regarded as a sequel of an acute organic reaction. The evidence is, however, lacking, that it is possible to distinguish in those cases that develop as a biogenic psychosis, an initial stage that can be more accurately described as an acute organic reaction than an acute stage such as commonly ushers in a biogenic psychosis. The fact remains that, whether *via* an acute organic reaction or not, mepacrine precipitates a chronic psychosis in about a fifth of the mental breakdowns attributable to it. The problem of differential diagnosis, therefore, comes to this: whether it is possible in the early stages to distinguish between the acute reaction to mepacrine and a chronic psychosis associated with it. The 5 cases suspected of being instances of biogenic psychosis precipitated by mepacrine comprise 3 cases of depressive state and one each of schizophrenia and mania. The former embrace the total number of cases of depressive state found in the series: at the end of 2 months one was showing schizophrenic development and the other 2 showed no improvement. They were older than the average for the series, their ages being 30, 37 and 43. The two going on to chronic depression gave a positive family history of insanity (father in the one case, sister in the other), and a personal history of life-long feeling of anxiety and inadequacy. The case of

mania developed into schizophrenia. In neither this case nor the one manifesting frank schizophrenia from the start was it possible to point to any features hinting that their prognosis was less favourable than that of the other cases of mania and schizophrenia in the series. The most that can be said, therefore, on the subject of differential diagnosis between a biogenic psychosis and an acute reaction precipitated by mepacrine, is that where the complex of symptoms is predominantly depressive in character the prognosis is less favourable and the condition is likely to become chronic, and that the condition was possibly a biogenic psychosis from the start.

There is not, when all is said and done, much to commend drawing a distinction between an acute reaction and a biogenic psychosis in the early stages of psychotic reaction to mepacrine. Even more unsatisfactory than regarding a case as one of biogenic psychosis, because the symptoms progress into chronicity, is that of calling it, in the final analysis, an organic reaction, when, in fact, the characteristic features of an organic reaction are absent. It is more rational to drop both terms, acute organic reaction and biogenic psychosis, and to diagnose a psychotic reaction to mepacrine simply as an acute reaction, which, because of its specific character in many instances, can, with truth, be termed a mepacrine psychosis.

Precautions in Use of Mepacrine.

Though there is ample statistical evidence that the risk of mepacrine psychosis is infinitesimal compared to the advantages that mepacrine yields both in the prophylaxis against, and treatment of, malaria, it nevertheless calls for alertness to the danger of mepacrine in the odd case. The circumstances which should put the medical attendant on his guard in exhibiting mepacrine are :

(*a*) Recent attacks of malaria (the more so when there has been more than one).

(*b*) Hepatic derangement.

(*c*) Injudicious over-dosage with prophylactic mepacrine.

(*d*) The presence of any factor that may delay the excretion of mepacrine, such as constipation, renal insufficiency, inadequate liquid intake or excessive fluid loss (Allen *et al.*).

The danger signals calling for the stoppage of mepacrine in the treatment of a malarial attack are :

(*a*) Staining of skin.

(*b*) Appearance of insomnia, alteration of conduct—restlessness, talkativeness—or confusion.

If the occurrence of the comparatively uncommon untoward effects of mepacrine are borne in mind, and the appearance of danger signs heeded, there is little risk in giving the dosage of the standard course. To exceed this dosage is, however, asking for trouble. Kingsbury appears to favour limiting the daily dose to 0·2 g. The U.S. Army medical consultants recommend that 0·7 g. as a suppressive dose, and 2·8 g. in 7 days, as a therapeutic dose, should not be exceeded.

Summary.

Thirty-three cases of psychosis associated with mepacrine have been reviewed. In about 70 per cent. a reaction, characterized by schizophrenic or manic or both manic and schizophrenic features, occurs. Depressive reactions are possibly instances of biogenic psychosis precipitated by it. Aetiological factors contributing to the toxic effect of mepacrine are considered. Figures are given for the time of onset of symptoms, their duration and the rate of recovery. The differential diagnosis is considered.

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SCHIZOPHRENIA IN A BOY OF 11 YEARS.

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THIS child developed signs of a serious mental illness during an attack of jaundice three years ago, just before his 11th birthday, and the condition has continued to develop up to the present time, though not quite evenly. At one period the illness was thought to have remitted, but it is evident in retrospect that the remission was, in fact, characterized by regression in behaviour and considerable invalidism. The clinical picture showed sustained mutism and one postural oddity as the most prominent features ; and in other respects the child showed an interest in his environment and participation in outside activities which in an adult with a similar diagnosis would be regarded as unusual. There was a morbid heredity in the case and a personality of distinctly pathological character which was clearly shown by his behaviour during his early years. The genesis of the reaction was complicated by an acute infective illness and by two head injuries, neither of which now appears to have been of importance, but which led to much clinical obscurity at the time. The anomalous clinical pattern and the inability of the child to communicate his experiences illustrate the difficulties of diagnosis at this age, and an attempt is made here to outline other possibilities which need consideration and the reasons in this case for rejecting them.

The literature dealing with schizophrenia in childhood is not abundant, and little agreement is evident as to the incidence or frequency of the condition. Lurie and others (1936) have drawn attention to this in a paper based on the survey of 1,000 behaviour problem children at the Child Guidance Clinic in Cincinnati which excluded all organic cases. These were sent to hospital primarily because of behaviour difficulties and not because of psychiatric abnormality in general, and they considered therefore that their own figures indicated that the incidence in general is probably higher than that indicated by the few reports available. Twenty cases (2 per cent.) were psychotic, and of these they considered 13 to be schizophrenic. Unfortunately only 2 case-histories are included in the report. Of equal uncertainty is the clinical pattern, and many writers have warned about the pitfalls in the diagnosis of this condition in childhood, and have attempted to formulate lists of symptoms which are thought to be characteristic of the disease. Bradley (1941) has laid down the following formulation : The child should be psychotic, should have become so after a period of normality, should show positive evidence of " withdrawal "—disturbed social contact ; and may show various secondary symptoms—anxiety, speech disturbances, bizarre conduct, and evidence of regression in behaviour. Bradley and Bowen (1941), in a survey of 138 behaviour disorders in children under 13, found 4 schizophrenics and 10

schizoid personalities, and found the most consistent and fundamental symptoms to be seclusiveness (with irritability if disturbed), bizarre behaviour, regression of interest, and sensitivity to comment or criticism. Seclusiveness with irritability was present in all 14 cases and not in the other behaviour disorders. Kasanin and Kaufman (1929) stress the importance of withdrawal and odd behaviour, and Lutz (1937) in a discriminating survey of his own and other cases stresses the importance of withdrawal from every-day contact with the environment. On the other hand Clardy and others (1941) brought all the resources of electroencephalography, air encephalography, and intelligence and personality tests to bear on 7 cases of presumed schizophrenia in an attempt to uncover or exclude organic factors, and these authors commit themselves to the doubt as to whether schizophrenia ever occurs before 10 years, and not even then if puberty has not been reached. Langfeldt (1937) shows a similar scepticism.

More specifically with reference to the case here described are observations on the significance of particular symptoms in children. Lutz (1937) noted speech disturbance to be frequent enough to be of value in diagnosis, and Homburger (1926) noted that prolonged speech disorder in children suggested schizophrenia. Creak (1939) mentions fastidiousness, insistence on orderliness, and stereotyped abnormalities of posture ; and she notes also the early and obvious difficulty of these patients in establishing normal relationships with other children. All these things were very clear in this case. Homburger (1926) stresses the pre-eminent importance of studying the development of the illness longitudinally in children if mistakes are to be avoided. He stresses the personality change in the child at the conclusion of each episode, the simplification and regression in speech and behaviour, and a tendency towards a more stereotyped type of thought and emotional response. As Potter (1933) points out, the thinking of a child is concrete rather than abstract, and the power of verbalizing is limited ; and delusions if present tend to be simple, naïve and unorganized, and the principal manifestations must inevitably be in the field of behaviour.

The mother of this boy was of the kind described by Despert (1938). She was aggressive, over-anxious and solicitous, at least in the early stages of the illness ; and the father was a subdued individual who hardly emerged at all in the family pattern. Evidence concerning the family is conflicting in the literature. Strecker (1922) thought the family situation and other environmental factors of little importance in schizophrenia, but Kasanin and Kaufman (1929), in a study of a series of cases which included 6 nuclear schizophrenics, found 2 foster children, 3 with shiftless, irresponsible fathers, and 1 with a brutal and alcoholic father.

Case history.—The patient is an only son with 3 sisters. His mother, as noted above, was of an anxious, solicitous type, though in the later stages of his illness she appeared to yield up hope of his recovery and reconciled herself very well to the situation. She had suffered from " hysteria " at the age of 20, and at this time she often used to wake suddenly from sleeping, fearing that the house was on fire. On several occasions she fell in the street and described herself as unable to move or speak, but aware of what was said to her. After a period of treatment in hospital these phenomena disappeared and she has not been affected since, except that she suffers from recurrent paroxysmal headaches. The maternal

grandmother is stated to have broken down mentally after a fall on her head, and would often have " blackouts," during which she rushed from the house. She died in a mental hospital in 1930. The patient's father formerly suffered from severe vertigo, which is now much better following an operation on the middle ear. He had in fact had several operations on this ear, and it is interesting to note at this point that the postural oddity shown by the patient was concerned with the protection of the ear on the same side as that on which his father had been troubled.

The birth was normal and the child walked at 13 months, talking if anything a little earlier than the average. After he went to school, at the age of 5, it was apparent that he was more timid and distrustful than others and that he was a solitary child. He preferred to play by himself, and expressed fear and dislike of " rough boys." He was terrified of dying, and required constant reassurance that the trivial cuts and scratches of childhood would not prove fatal; and he was terrified of water, and consistently refused either to paddle or to bathe. He was teased by his sisters and responded with tears, and his schoolfellows called him a " sissy." His parents were unable to induce him to make friends, and if excursions with other boys were arranged he would leave them and return home. During air raids he was not apparently afraid but talked continuously and excitedly. When evacuated with his sister, however, he is reported to have been white and shaken and " transfixed with fear " when the time came for him to leave home.

His Headmaster reports him as above average in intelligence, and he had reached standard 7 before leaving school at the time of his illness. A battery of intelligence tests given to him at an early stage in his illness at a time when he was not mute rated him as superior. During childhood he contracted successively measles, chicken-pox, and whooping cough, not severely, and without any unusual features that might suggest an encephalitis. In 1943 he is stated to have collided with another boy during a race and to have been unconscious for 4 minutes. For the remainder of the day he was " drowsy and stupid," but appeared quite well by the next morning.

The first indication of illness occurred during a mild attack of infective hepatitis in March, 1944, just before his 11th birthday. For no organic reason that could be discerned he complained of his eyes and insisted that the room be darkened. He almost stopped eating, lost a good deal of weight, and, being regarded as a case of anorexia nervosa, he was removed to hospital. After 3 weeks he was much better and went away to the seaside for convalescence, which was terminated abruptly by the fact that he refused to speak or to open his eyes, over which he held his hands. He improved, however, and a few weeks later returned to school, where he remained until November, 1945. During this time he showed no very marked positive abnormalities other than an accentuation of his personality traits—seclusiveness, suspicion and timidity. In November, 1945, however, he was struck on the head with a football (not apparently with great force), and thereafter he became dreamy and vague, put his hands over his eyes again and had to be taken from school. It appears that he did not see daylight for the next 11 weeks, refused to eat from time to time, screamed if he was touched, seldom spoke, and sat all day long in his chair, being dragged or carried about the house when it was necessary to move him. In February, 1946, his family could stand this no longer, and he was admitted to hospital. The notes covering that admission state that he lay in bed with his eyes tightly closed, resisting any attempt to move his limbs, and crying quietly when the attempt was made. One electro-shock was given without improvement, and it was noted at that time that his attitude was resumed an appreciable time before consciousness was regained. Late in July, 1946, he improved dramatically, and in September he was discharged. There was, however, a notable degree of regression in his conversation, which was of a standard well below that which he had previously attained. A representative sample was, " It will be nice at home in me little chair, drinking me little glass of milk, wiv me muvver to look after me."

In October, 1946, he complained of pain in his ear (on the same side as his father's lesion had been), and refused to attend occupational therapy which had been arranged for him or to see a doctor. He insisted on wearing a woollen helmet covering most of his face night and day. When seen by the writer as an out-patient in January, 1947, he had not spoken for 11 weeks, he had screamed and kicked if interfered with, and had made several unprovoked attacks on little girls in his neighbourhood.

He was admitted to hospital on 8 January, 1947. He was mute, and wept if pressed to speak—quietly, copiously, and without apparent distress. He took a hand held out to him and grasped it tightly, as though in need of sympathy, and was quite obedient to any direction except that he should speak. Narco-analysis with sodium amytal was undertaken, and during this a number of stereotyped movements were manifested—he beat his chest and made signing movements with his hands—but could not be induced to speak, nor was any rapport established at any point. There were no technical difficulties, and the failure was certainly a function of the illness and not of the technique. He was examined carefully as an aphasic might be tested, and no abnormality was apparent. He would, for example, select objects the names of which were shown to him on cards, and use them correctly, except that he showed great aversion to a pencil and would not write or make any mark on paper.

In the ward he was generally liked. He was mischievous, but pleasantly so, not averse to gentle horse-play, and able to play draughts and cards. His woollen helmet was taken from him and instead he kept one hand permanently over his ear, without apparent fatigue. This was never taken down for any purpose—he played whist, bathed, ate and slept with it in place. During sleep the hand was undermost, but it was never observed away from his ear. He befriended the ward cat and appeared very attached to it. He showed both interest and curiosity in ward activities, but showed no kind of emotional warmth, and was certainly less active physically than is normal at 13 years. An interesting feature was the meticulous care he bestowed on his clothes, particularly in the matter of the creasing of his trousers, which he placed carefully under the mattress every night. Unfortunately his response to the presence of other children could not be studied.

Late in February treatment by insulin shock was begun. After the first coma he talked for the first time, repeating " Oh dear, Oh dear " several times until the clouding disappeared. During coma his hand came away from his ear, but returned as his sensorium cleared. In the ensuing days, after termination with glucose, he expressed the feeling, " I want to wake up a proper lad; let me hear proper voices, not these voices all around me. I want to get out of this trance, they are playing jokes on me." He screamed loudly at about these times, like a soul in anguish, and it was indeed hideous to hear him. His mental content could not be studied satisfactorily except by his spontaneous utterances. Answers to questions were confused by his echolalia, stereotyped repetitions, and by his great suggestibility. Questions of the kind used with adult schizophrenics elicited quite misleading answers, as would be expected in a regressed child in whom the content was of a very unorganized and simple kind. It is interesting to note that in sopor, when approaching coma, so strongly was his hand held to his face that his weight could be lifted by it. With the onset of coma the hand came away easily and remained by his side. Late in April, in the face of failure to show any improvement, insulin treatment was abandoned, and his condition has remained unchanged since.

X-ray of his skull was repeated on 2 occasions, and was negative. Neither biochemical investigation (17 ketosteroids, etc.) nor electro-encephalography gave results outside the range of normal.

Differential diagnosis.—A neurotic reaction was a clear possibility, especially in view of the apparent friendly relationship the patient was able to establish with adults. Homburger (1926) noted that voluntary silence might occur for very long periods in neurotic children, and Hutter (1939) describes what he calls a psychotic reaction in a psychopathic type in a girl of 15 years, who required artificial feeding for months, and who was mute, negativistic, and showed stereotypies. This case made a good recovery and was discharged, and he differentiates the reaction as a " leichtere psychose," not very helpfully perhaps on the grounds of " nicht wollen," as opposed to " nicht können." This possibility was rejected in this case in view of the length of the history, the totality of the disability, and the positive symptoms which have been described.

Heller's disease requires some consideration. This group of diseases, as it

is likely to be, was described by Weygandt in 1908, and by Heller a little later with a definition of the syndrome by Zappert in 1921 ; and syndromes more or less similar were described by de Sanctis (1925) and Constantini. The whole question is reviewed by Bovet (1938), who describes a case and stresses the other diagnostic possibilities—post-encephalitis, epiloia, epileptic dementia, and infantile schizophrenia. Bovet does not believe the disease to be an entity, and notes that similar symptoms may occur in juvenile syphilis, post-pertussis encephalitis, trauma, and post-encephalitis. Bovet's own case, it may be noted, was associated with epilepsy. This case, however, falls into an older age-group than that described for Heller's disease, and has not deteriorated with the rapidity always noted in these cases.

Post-encephalitis is a possibility always to be considered, and the absence of neurological signs even at this stage would not of itself eliminate the possibility (Kasanin and Petersen, 1926). No history of acute encephalitis lethargica was forthcoming, but this, too, would not be sufficient. On the other hand, most descriptions have emphasized the hyperkinetic nature of the clinical picture—restless over-activity, emotional lability, impulsiveness and insomnia. Nevertheless, though unlikely in this case, it remains a possibility which only time will eliminate, and Kasanin and Petersen (1926) suggested that mild cases with barely noticeable onset might leave a residual psychosis apt to be diagnosed as schizophrenia, or depression. Encephalitis after the infectious diseases of childhood also usually shows a hyperkinetic pattern (Smith and Trapp, 1944), and here again the history gave no indication of such an event.

Three other possibilities were considered. Of these a severe cyclic depression was rejected. Kasanin and Kaufman (1929) thought it very rare, and when present clear cut and easily differentiated. The onset during jaundice raised the possibility of Kinnier Wilson's disease, but the picture is not at all characteristic, and examination showed no sign of Kayser-Fleischer rings or other abnormalities. The remaining possibility is epileptic dementia, and Kennedy and Hill (1942) draw attention to the possibility of a cortical dysrhythmia without actual fits yet leading to dementia. In their case the diagnosis by electro-encephalography (which showed paroxysmal spike and wave amongst other abnormal features) was confirmed a year later by the appearance of convulsions. The EEG in this case, however, gave no clear-cut information, and there was no evidence to suggest such a diagnosis.

Other possibilities eliminated, it remains to consider the positive evidence of schizophrenia. Adopting (after Campbell, 1925) withdrawal as a fundamental feature, if anything is, of schizophrenia, there were several interesting features about this boy. In a psychobiological study of withdrawal Angyal (1940) describes lack of interest, apathy and indifference as characteristic of the psychological element. It might be said this boy showed interest in the ward games, made friends with the cat, was well aware of what went on around him, and played cards. And yet, can anything be fundamentally more withdrawn than mutism not due to aphasia or anarthria, for his ability to speak from the neurological point of view was well shown during the insulin treatment? Not only was he mute, but no substitutive activity was shown.

He made no attempt to write or to sign or to make any active purposive contact with his fellows. Language or something to replace it is of the highest importance in social integration, and yet this patient had abandoned it. He adopted, and has maintained a stereotyped attitude with his left arm for months at a time, an attitude which to us is meaningless, and is possibly equally so to himself. Under sodium amytal a number of stereotyped movements, devoid of obvious meaning, were liberated, and in hypoglycaemia his speech was impoverished, repetitive, and gave evidence of hallucinosis and paranoid feelings, though the importance of these is hard to assess in that they were only evident in a state of clouded consciousness. Emotionally he appears bleached, and the occurrence of quiet circumscribed weeping not obviously associated with any feeling of grief and only precipitated by interference does nothing to alter the impression.

The prognosis of schizophrenia at any age is in general not very good, and in childhood it is gloomy indeed (Despert, 1938). In this case it could hardly appear less enlightened by any ray of hope in view of the steadily increasing social disability and the length of the history, which is now over 3 years.

Summary.

(1) A case of schizophrenia with mutism in a child of 11 years is described and the differential diagnosis is considered.

(2) A positive family history of mental abnormality and a morbid prepsychotic personality were outstanding features in the case.

(3) The symptomatology was anomalous, and illustrates the difficulty of diagnosis at this age, except in the light of the development of the illness over a long period.

(4) There was no response to any form of treatment.

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TREATMENT OF EPILEPTICS WITH EPANUTIN.

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Modern treatment of epilepsy is directed towards (1) the control of the fits, and (2) the diminution or abolition of the underlying cerebral dysrhythmia.

In this paper I shall give my personal observations on 196 patients treated with epanutin in the Maghull Colony over a period of 6 years.

Dosage and Tolerance.

The average optimal adult dose consists of 1 capsule of gr. 1½ given 3 times daily after meals (to prevent gastric disturbances), and I have found that children from 10 years of age upwards can tolerate the adult dose; in the case of younger children caps. epanutin gr. ¾ *t.d.s.* is ample.

Sometimes the daily dose of 3 capsules brings little or no improvement. Yet the addition of a further capsule may abolish the fits altogether.

In one patient, after a period of freedom from fits, the daily dose was reduced from 4 to 3 capsules. The fits then began to recur. Restoration of the dose of 4 capsules abolished them once more.

In other cases, where epanutin alone has not succeeded in completely stopping the attacks, the addition of a nightly tablet of luminal—varying from ½ to 1½ gr., depending on the age of the individual and the nature of the fits—has given most satisfactory results.

Quite a few patients showed little response to 4 capsules daily, but did well on 5.

The Change-over.

In substituting epanutin for other anti-convulsants, viz. bromides, luminal, etc., we usually begin with one capsule the first day, 2 capsules the next, and 3 capsules the next.

The following day a gradual reduction is begun in the dosage of the previous drugs, e.g. one of the 3 doses of bromide mixture is omitted daily, and then the dose of luminal (if any) is reduced by ½ gr. at a time—until the patient is taking nothing but the 3 capsules of epanutin (Coope and Burrows, *Lancet*, March, 1940).

Clinical Observations.

Of 196 cases treated, 127 showed definite improvement.

59 showed reduction in total number of attacks.

48 responded to treatment in the first year.

6 ,, ,, 2 years.

5 ,, ,, 3 ,,

32 had immediate cessation of attacks after commencing epanutin, and remain free.
3 showed gradual reduction over 1–6 years.
4 had no attacks after increasing to 4 capsules daily.
1 showed improvement after reduction to alternate doses of 3 and 4 capsules daily.
12 showed improvement following the addition of luminal *nocte*. (One had no attacks following the addition of luminal, and has remained free.)
2 showed reduced minor attacks only.
15 ,, mental improvement without greatly reducing the number of attacks.

Epanutin Discontinued in 69 Cases.

4 showed increased number of attacks.
21 developed mental symptoms immediately on the establishment of the optimal dose (climbing up walls, walking on all fours).
2 developed mental symptoms at 1 year.
1 ,, ,, ,, 2 years.
1 ,, ,, ,, 3 ,,
5 ,, rashes (1 scarlatiniform, 3 morbilliform, 1 purpuric).
12 ,, vertigo, diplopia and blurred vision.
12 ,, tremors, staccato speech.
1 ,, depression and confusion.
3 ,, ataxia.
4 ,, vomiting.
1 ,, stupor.
2 became quarrelsome.

Twelve Selected Cases.

Case 1 (R. D—).—A young woman, 23 years of age, had " uncountable sensations " and one major attack in 1940.

She was put on epanutin 1 capsule *t.d.s.* in March, 1941.

The following year she had one major attack, and the " sensations " completely disappeared.

She had no further attacks (major or minor), and from being a lazy girl, she became bright and alert.

She is now earning her own living in London.

Case 2 (N. T—).—A young woman, 39 years of age, first consulted me 6 years ago. From the age of 14 she had been having an average of 6 major attacks per month. They were very severe in character, and she was constantly injuring herself (and her aged mother who looked after her).

She could not get off a chair unaided.

She was extremely dull and lethargic.

Treatment had consisted of bromide mixtures and luminal gr. 2 *nocte maneque*.

I decided to try her with 1 capsule epanutin gr. 1½ *t.d.s.*, with amazing results.

She has never had another fit. Her whole disposition has altered, and she has now become a happy, contented and useful member of society. She has taken complete control of all household duties, is a regular member of the local church choir, goes to the cinema, and is taking lessons in pianoforte playing. She has

had her hair permanently waved, and has been fitted with spectacles and artificial teeth.

In short—she has taken a new lease of life.

Apart from the fact that she shows some loss of weight, there have been no toxic symptoms.

Case 3 (M. E—).—During the year 1943 a young woman (aged 28 years) averaged 6 major attacks per month.

In May, 1944, I put her on 1 capsule epanutin *t.d.s.*

Her attacks stopped immediately, and she has remained free. She is a bright, vivacious girl, always singing about the home, trying to make others happy.

She shows a slight degree of hyperplasia of the gums, and there is a slight loss in weight.

Case 4 (J. T—).—This middle-aged man was admitted to the Colony in 1946, with a history of numerous severe major and minor attacks in 1945.

He was put on epanutin on admission.

The following month he had 1 major and 7 minor attacks, but none since.

He has become much brighter in every way, and is most efficient in his employment as a nurseryman.

Case 5 (S. G—).—This young man was put on epanutin on his admission to the Colony in March, 1942. In the 9 remaining months of that year he had 6 major and 7 minor attacks.

He was increased to 4 capsules epanutin in 1943, with remarkable results.

	Major.		Minor.	
In 1944 he had	0	.	1	attack.
,, 1945 ,,	0	.	0	,,
,, 1946 ,,	0	.	0	,,

He is a bright, active man, and hopes very shortly to leave to earn his living.

Case 6 (D. B—).—This patient—a young man of 18—was tried on 3 capsules of epanutin daily in 1940.

	Major.		Minor.	
In 1940 he had	0	.	6	attacks.
,, 1941 ,,	0	.	12	,,
,, 1942 ,,	0	.	24	,,
,, 1943 ,,	8	.	10	,,
,, 1944 ,,	11	.	0	,,
,, 1945 ,,	6	.	0	,,
,, 1946 ,,	0	.	0	,,

In March, 1945, epanutin increased to 4 capsules daily.

No further attacks.

(The next 6 cases show the response to epanutin by children, whose ages range from 9 to 15 years.)

Case 7 (S. P—).—A girl (11 years).

	Major.		Minor.	
In 1944 (9 months) she had	7	.	24	attacks.
,, 1945 ,,	57	.	23	,,
,, 1946 ,,	2	.	9	,,

Put on epanutin gr. 1½ *b.d.s.* on 4 January, 1946.

No attacks since 9 January, 1946.

IQ/BE.		IQ/FE.		Wt.
95	.	98	.	+ 6 lb.

Case 8 (J. M—).—A girl (15 years).

	Major.		Minor.	
In 1945 she had	30	.	14	attacks.
,, 1946 ,,	0	.	0	,,

Put on epanutin gr. 1½ *t.d.s.* in December, 1945.
Attacks stopped immediately.
None since.

IQ/BE.		IQ/FE.		Wt.
87	.	86	.	+ 11 lb.

Case 9 (L. S—).—A girl (9 years).

	Major.		Minor.	
In 1946 (9 months) she had	84	.	174	attacks.
,, 1946 (3 ,,) ,,	0	.	8	,,

Put on epanutin gr. ¾ *t.d.s.* and luminal gr. 1 in September, 1946.

IQ/BE.		IQ/FE.		Wt.
85	.	92	.	+ 3 lb.

Large reduction in major and *minor* attacks.

Case 10 (F. A—).—A boy (12 years). Admitted 12.xi.42.
Put on epanutin gr. ¾ *t.d.s.* in June, 1943.

	Major.		Minor.	
In 1943 he had	52	.	3	attacks.
,, 1944 ,,	39	.	4	,,
,, 1945 ,,	13	.	0	,,
,, 1946 ,,	0	.	0	,,

In 1945 he was put on the adult dose epanutin gr. 1½ *t.d.s.*
Since then he has greatly improved both physically and mentally (IQ unchanged).

IQ/BE.		IQ/FE.		Wt.
100	.	100	.	− 4½ lb.

No attacks in 1946.

Case 11 (R. C—).—A boy (15 years) was admitted on 17.vi.43.
Previous to admission he was having a large number of major and minor attacks, although he was on epanutin gr. ¾ *t.d.s.*
In June, 1943, he was increased to gr. 1½ epanutin *t.d.s.* There was a marked general improvement.

	Major.		Minor.	
In 1944 he had	0	.	1	attacks.
,, 1945 ,,	1	.	1	,,
,, 1946 ,,	0	.	0	,,

IQ/OE/E.		IQ/FE.		Wt.
72	.	76	.	+ 8¼ lb.

No attacks in 1946.

Case 12 (C. B—).—A boy (15 years) was admitted on 13.v.41.
Epanutin was tried soon after admission but discontinued because of dizziness. Tried again in 1943—no recurrence of dizziness but a slight gingivitis. Great improvement generally.

	Major.		Minor.	
In 1942 he had	0	.	504	attacks.
,, 1943 ,,	0	.	609	,,
,, 1945 ,,	0	.	0	,,
,, 1946 ,,	0	.	1	,,

A striking example of the very few instances where epanutin reduced the number of minor attacks.

IQ/BE.	IQ/FE.	Wt.
91	81	+ 9 lb.

(IQ = Intelligence quotient. BE = Before epanutin. FE = Following epanutin. OE = Already on epanutin.)

Weights.

It has been generally believed that patients put on epanutin show a loss in weight.

The following table may prove of interest.

	Numbers.	Gain in weight.	Loss in weight.	Stationary weight.
Men	56	26	22	8
Women	28	2	23	3
Boys	15	14	1	—
Girls	15	14	—	1
Total	114	56	46	12

It will be noticed that there is a greater tendency to lose weight by adult patients—females more so than males. In one of the women's homes 9 out of 9 patients on epanutin lost weight, and in another 8 out of 11 women lost weight.

In the children's homes on the other hand 14 out of 15 boys and 14 out of 15 girls gained weight.

Intelligence Quotients.

One would expect that an improvement in the physical and mental condition due to a reduction of fits under epanutin therapy would produce a rise in the IQ.

Of 30 children tested only 7 showed a higher IQ reading.

The explanation may lie in the fact that, though the convulsive explosions have been abolished, inhibited, or reduced by epanutin, the cerebral dysrhythmia referred to in the introduction may still exist, thus causing a blunting of the intelligence centres in the brain with a consequent lowering of the IQ.

Electroencephalographic recordings may throw some light on this perplexing matter.

Hyperplasia of the Gums.

This was present in 6·6 per cent. of the 196 cases treated, and occurred in spite of careful oral hygiene.

Prior to the administration of epanutin it had not been observed.

It was mostly of a mild type and, in itself, did not require a withdrawal of the drug.

Some cases responded quite well to vitamin C and calcium lactate tablets.

Urinary System.

Transient albuminuria was present in one patient who suffered from recurrent attacks of tonsillitis.

In about 20 per cent. of the urines tested the reaction was alkaline.

Effects on Mentality.

(a) *Beneficial.*—Many patients who, on prolonged bromide and barbiturate administration, showed signs of cerebral stagnation, and often mental deterioration, evinced a remarkable transformation when switched over to epanutin.

Patients who for years had been living in an atmosphere of apathy and introspection suddenly blossomed out into happy, carefree individuals.

Some who had been quarrelsome and difficult to manage took on a mantle of geniality, whilst others, once subject to periodic "brainstorms" became quite docile and pleasant.

(b) *Deleterious.*—In some cases epanutin has had an adverse effect, causing marked mental symptoms such as climbing up walls, walking on all fours, depressed and confused states, etc., as I have previously mentioned, and these usually take place in the very early stages of epanutin administration.

These distressing features disappear on the withdrawal of the drug.

Fatalities.

During the course of treatment 4 patients died, viz. 2 from diffuse broncho-pneumonia following status epilepticus, one from purpura haemorrhagica and one from hyperpyrexia.

Case 1.—A woman patient, 31 years of age, on being changed over to epanutin following a batch of major fits, became very exhausted and complained of dizziness.

Epanutin was then replaced by bromides and chloral, but without effect, for in the following 24 hours she had 15 attacks. Though she had no further fits, she developed a broncho-pneumonia from which she subsequently died.

Case 2.—A young man, 18 years of age, averaging 10 major and 3 minor attacks per month, had for a number of years been kept on bromide and luminal.

It was decided to try him with caps. epanutin gr. 1½ *t.d.s.* A fortnight later he had 2 major attacks, after which he was free for 2 weeks.

Then his attacks came 2 → 4 → 19.

Epanutin was increased to 4 capsules.

There were no further attacks, but the temperature rose to 102° F. → 105° F., and the patient died from diffuse broncho-pneumonia.

Case 3.—A male patient, 31 years of age, had been for 9 years on bromides and luminal, but because of his lethargic state we decided to change him to epanutin gr. 1½ *t.d.s.* in July, 1941.

He definitely improved until 24 August, 1943, when he developed external and internal haemorrhoids which bled rather freely. There were no other clinical signs.

The urine was normal, s.g. 1012, reaction acid, no albumen.

Four days later he developed a purpuric eruption on different parts of the body, fingers, back of neck, right axilla, accompanied by a sudden profound degree of anaemia.

He was transferred to the Liverpool Royal Infirmary, where he died on 31 August, 1943.

Case 4.—A girl of 16 was admitted on 8.iii.44 suffering from major and minor attacks of epilepsy.

Being rather hysterical she was first tried on a bromide, borax and valerian mixture with luminal gr. 1 at night, but her attacks increased, and she had a large number of minors which appeared to take a lot out of her.

On 27.v.44 I decided to try her with epanutin.

The latter appeared to modify her attacks, but with the onset of her first menstrual period on 13.ix.44 she had a batch of 28 very severe major attacks, and her temperature suddenly flared up, and within an hour showed an axillary reading of 107·4° F. (8 p.m.).

By tepid sponging the temperature was reduced to 106° F. (9.30 p.m.), but the patient died at 12.15 a.m.

The temperature rose again after death.

Unfortunately in all these cases it was impossible to obtain a post-mortem examination.

Summary.

The results of treatment of 196 patients in the Maghull Colony with epanutin have been described, and I shall briefly tabulate my findings and observations.

	Per cent.
Definite improvement	65
Total cessation of attacks	16
Gradual reduction of attacks (over 6 years)	1·5
Reduction in total number of attacks	30
Reduction in number of minor attacks	2
Mental improvement (without greatly reducing attacks)	7·6
Toxic symptoms developed in	30
Mental (13 per cent.) { Immediate	10
Mental (13 per cent.) { Remote	3
Rashes	2·5
Vertigo, diplopia and blurred vision	6
Tremors and staccato speech	6
Hyperplasia of gums	6·6
Depression and confusion	0·5
Stupor	0·5
Ataxia	1·5
Vomiting	2

I wish to acknowledge the invaluable help I have received from Dr. Robert Coope, Consulting Physician to the Maghull Homes for Epileptics (Inc.), from Miss Dutton (Lady Superintendent), Miss Ingham (Head-mistress of our Special School), and from the matrons of the individual houses in the Colony.

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* A number of abstracts in this section are reproduced from *Chemical Abstracts* and *Psychological Abstracts*. To the Editors of these Journals we extend our grateful thanks.

Audiogenic Fits Produced by Magnesium Deficiency in Tame Domestic Norway Rats and in Wild Norway and Alexandrine Rats.

1. Domestic and wild Norway rats and wild Alexandrine rats on a magnesium-deficient and control diet were tested on alternate days with an air blast for susceptibility to audiogenic seizures. All the rats on the magnesium-deficient diet had fits, while not one of the control animals had a fit.

2. Domestic Norway rats fed the magnesium-deficient diet began to have running fits in an average of 8 days (range 3 to 16); wild Norways in an average of 15 days (range 5 to 30); and wild Alexandrines also in an average of 15 days (range 9 to 24).

3. Magnesium-deficient domestic Norways died usually during their first fit, and none survived more than four fits. Wild Norways and Alexandrines had between 6 and 19 fits, but none of them died during the entire test period of 50 to 55 days. (Author's abstr.)

The Effect of Experimental Insomnia on the Rate of Potential Changes in the Brain.

The changes in the potential pattern of the brain have been quantitatively studied during prolonged wakefulness and during mental activity. It was found that:

1. The EEG, quantitatively analyzed on the basis of per cent. time frequency distribution, affords an accurate objective method of studying the effect of mental activity and of the fatiuge of prolonged wakefulness.

2. Changes in the state of attention or alertness as produced by a mental multiplication problem cause an increase in the rate of the electrical activity of the brain. The changes are regular and the extent of the increase parallels the intensity of the mental effort.

3. Increasing periods of experimental insomnia also result in a progressive increase in the rate of the potential changes in the brain.

4. Superimposing an additional mental effort during experimental insomnia results in irregular changes indicating that the capacity of the fatigued brain to further increase its rate of electrical activity in response to such stimulus is reduced.

5. The changes produced by mental activity and by sleeplessness are in the same direction, although under the conditions of these experiments, not of the same magnitude. This is interpreted to indicate that mental effort required either for working a problem or in staying awake during experimental insomnia produces an increase in the rate of the electrical activity of the brain.

(Authors' abstr.)

Effect of Frontal Lobectomy on Blood Sugars of Normal Cats and Monkeys and Adrenal Denervated Cats.

A. In cats in which sham rage can be produced by bilateral frontal lobectomy:

1. The blood-sugar level under dial or nembutal anesthesia is increased within one half-hour following frontal lobectomy, and may continue raised for at least 4 to 5 hours thereafter.

2. No such rise in blood sugar occurs in cats which are anesthetized with barbiturates without frontal lobectomy.

3. Bilateral removal of an amount of occipital lobe approximately equal to that of bilateral frontal lobectomy causes no such rise in blood sugar.

4. There is an accompanying rise of pulse and respiratory rate when blood sugar rises.

5. Previous adrenal denervation causes the blood sugar rise which appears after frontal lobectomy to fall within 3 to 4 hours.

6. No rise in blood pressure occurs after frontal lobectomy although blood sugar, pulse and respiration increase.

B. In monkeys, which do not develop sham rage after cortical ablations, there is no significant change in blood sugar, pulse, respiration or blood pressure after bilateral frontal or occipital lobe ablation. (Authors' abstr.)

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The Use of Electric Shock Therapy in Psychoneurosis.

Fifty patients suffering from psychoneurosis had treatment supplemented by electric shock in the 3-year period between 1942 and 1944. Those patients whose symptoms were largely anxiety, tension and depression were most benefited. Thus among those with reactive depressions 9 of 11 recovered. Of those with anxiety conditions 10 of 12 were recovered or much improved. Seventeen of 18 suffering from a mixed psychoneurosis were similarly benefited. Of the compulsive obsessive group, 4 were markedly benefited while 4 were improved and 1 unimproved.

These results have been compared with those obtained in the earlier mentioned group of 200 psychoneurotic patients whose treatment was not supplemented by electric shock. There was a distinct difference between the two groups in the average length of hospitalization. In the shock-treated group it was $5\frac{1}{2}$ months while in the non-shock-treated group it was $8\frac{3}{4}$ months. Thus the period of hospitalization of those who received electric shock was less than two-thirds that of the group treated in the pre-shock era.

Thirty-nine per cent. of the 200 non-shock-treated patients and 46 per cent. of the 50 shock-treated patients recovered. This is not an impressive difference considering the discrepancy in the numbers involved. However, 80 per cent. of the shock-treated group were home recovered or much improved, that is distinctly benefited, while but 59 per cent. of the non-shock-treated group were so benefited. Of the 200 patients, 151 received some benefit from treatment while 48 of the 50 shock-treated patients were so considered. (Author's abstr.)

An Evaluation of Shock Therapy.

In view of these findings, it becomes imperative that shock studies concentrate on investigating the readmission and deteriorating aspects of shock therapy. The findings tend to indicate that shock therapy increases the frequency of readmission and thus raises the question of whether the time saved in the hospital at the first admission is not lost by the early readmission following shock treatment. This is particularly significant since it seems likely that shock therapy does produce

deterioration and personality changes which may explain this increased readmission frequency. It is hoped that this paper may stimulate some research in this direction and that more extensive studies will be made. (Author's abstr.)

Brain Metabolism in Man : Unanesthetized and in Pentothal Narcosis.

1. The effect of pentothal anesthesia was examined in 9 subjects on whom 19 observations were made. Blood was drawn simultaneously from the right and left internal jugular veins and the femoral artery in order to determine the right and left cerebral arteriovenous oxygen differences and the right and left cerebral blood flows, which were measured according to the method of Kety and Schmidt to calculate cerebral metabolic rate. When results from both right and left sides are averaged, the oxygen consumption of the brain in the unanesthetized man is 3·3 c.c. oxygen/100 gm. of tissue/minute. This value, however, represents two groups : a higher one with 3·9 c.c. oxygen/100 gm. of tissue/minute and a lower with 2·7. Because of the asymmetric venous return, the cortical component usually appears preponderantly in one of the two internal jugular veins and it is concluded that the portion of the brain with the higher metabolic rate is the cortex.

2. In every instance pentothal anesthesia induced a depression in metabolic rate. The average during the second and third stages of anesthesia is 2·1 c.c. oxygen/100 gm. of tissue/minute, a reduction of 36 per cent. from the control value. The pattern of pentothal anesthesia shows that cortical oxidations are depressed earlier and more profoundly than those of the rest of the brain, which in turn may also be subjected to metabolic inhibition.

3. Because of some effects of pentothal, which cannot be attributed to metabolic inhibition, it is concluded that pentothal narcosis is on a bipartite basis, including metabolic depression as one factor and inhibition of nerve function as another. The clinical signs of pentothal narcosis can be best explained on this bipartite basis.

4. In the resting individual, the high metabolism of the cortex is correlated with its rapid blood flow. It is probable that the parts of the brain with the higher metabolic rates possess a greater vascular complement and that this is a structural adaptation to metabolic requirements. On the other hand, the retarded cerebral blood flow observed with pentothal anesthesia is functional and in part is a response to a decreased metabolic rate. The depression of metabolism induced by pentothal alters both the cerebral arteriovenous oxygen difference and cerebral blood flow. In most instances, both are decreased and, therefore, each of these factors is modified to account for the fall in cerebral metabolic rate. (Authors' abstr.)

Psychological Factors in Men with Peptic Ulcers.

Twenty men with peptic ulcers were studied from the psychosomatic point of view. None were psychologically mature. All of them had strong dependent desires which were secondary to either rejection or spoiling in early childhood. One group utilized the mechanism of over-compensation to deny these desires, resulting in the overt character picture of the driving, hard-working, ambitious business man. However, the authors found that the majority of their patients in a charity hospital were either outwardly passive and effeminate or openly acted out their deep oral desires. Ulcer symptoms developed in all of their patients as responses to frustration of these cravings, when the various defense mechanisms they used to handle such conflicts proved inadequate. (Authors' abstr.)

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Cerebral Anoxia from High Altitude Asphyxiation: A Clinicopathologic Study of Two Fatal Cases with Unusually Long Survival and a Clinical Report of a Non-fatal Case.

Three cases of anoxic anoxia occurring in aviators while engaged in combat are presented in detail. In 2 cases the anoxia proved fatal in 40 hours and 3 weeks respectively, and in the third instance the patient was observed for a period of 3 weeks and was then transferred to the United States. The degree and duration of anoxia in each case are not completely known. In the first, the accident occurred at an elevation of " more than 20,000 feet," the patient being found unconscious 5 minutes after completion of a bomb run, at which time resuscitation was commenced. In the second, the patient was exposed to an atmosphere at 24,000 feet for approximately 10 minutes. In the third, it was at 27,000 feet that the oxygen tank of the plane was shot away, necessitating a rapid descent to 7,000 feet, during which time no effort could be made to revive the patient.

In the case of approximately 40 hours' duration (Case 1) a conspicuous necrosis of ganglion cells was observed in laminas III to VI of the cerebral cortex, the striatum, the cerebellum, Sommer's sector of the hippocampus and the anterior horns of the spinal cord, mostly focal in character, and degeneration of myelin in the internal capsule. Also observed were early proliferation of the fixed tissue cells of the leptomeninges and vascular adventitia and mild exudation of lymphocytes and neutrophils into the meshes of the arachnoid, the perivascular spaces, and, to a limited extent, the parenchyma of the brain. In the case of 3 weeks' duration (Case 2) the changes were of virtually the same location except that the cerebral white matter, brain stem and spinal cord were relatively spared. The profound damage in these cases of sudden and severe anoxic anoxia is strikingly similar to that observed in some of the other forms of anoxia. (Authors' abstr.)

Incidence of Anisocoria and Difference in Size of Palpebral Fissures in Five Hundred Normal Subjects.

Five hundred neurologically normal persons were studied with reference to the incidence of anisocoria and of differences in the width of the palpebral fissures. Nearly 17 per cent. of the patients showed a slight but perceptible anisocoria. In 4 per cent. the difference in pupillary size was pronounced. Inequality of the palpebral fissures of a slight degree was noted in nearly 36 per cent. of the patients. Pronounced differences were noted in nearly 6 per cent. When both the pupils and the fissures were unequal, the smaller pupil and the narrower fissure were on the same side in 77 per cent. of the patients. However, in nearly one-half the patients with anisocoria the fissures were equal, and inequality of the fissures was accompanied with equality of the pupils in 73 per cent. of the patients, revealing unequal fissures. Consequently, inequality or imbalance of sympathetic innervation could be held responsible for at least some instances of the observed anisocoria, but in general, no gross factor could be identified as responsible for any asymmetry of sympathetic stimulation. In other instances differences in errors of refraction may play a role in causing unequal pupils. The incidence of inequality of the palpebral fissures is relatively high, and mild degrees may be considered without significance. Anisocoria should never be dismissed as an anomaly until a thorough search reveals no etiologic basis for it. (Author's abstr.)

Relation of Mental Imagery to Hallucinations.

The mental imagery of 40 patients with schizophrenia, 10 patients who had recovered from an alcoholic hallucinosis, and 114 normal subjects was tested.

Schizophrenic patients with auditory hallucinations were found to have a significantly lower mean percentage of auditory imagery than either normal subjects or schizophrenic patients without auditory hallucinations. The normal subjects and the schizophrenic patients without auditory hallucinations did not differ significantly in this respect.

Patients who had recovered from auditory hallucinosis were found to have a significantly lower mean percentage of auditory imagery than normal subjects. The mean percentages of auditory imagery for patients who had recovered from an alcoholic hallucinosis and for schizophrenic patients with auditory hallucinations did not differ significantly.

Not only do these findings disprove the old theory that auditory hallucinations are exaggerations of predominating auditory imagery, but they suggest the new concept that one of the factors responsible for auditory hallucinations is relatively deficient auditory imagery. (Authors' abstr.)

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Prefrontal Leucotomy : A Neuro-anatomical Report.

An anatomical study of 7 leucotomized and 1 lobectomized human hemispheres has led to the following results :

(1) The anteromedial nucleus of the thalamus projects to at least the pre-callosal part of the cingulate gyrus ; the anteroventral nucleus to more posterior parts of the cingulate gyrus ; and the axial orientation of this projection in at least anteromedialis is the same as in animals.

(2) There is some evidence that pars magnocellularis of the dorso-medial nucleus of the thalamus projects to only the medial half of the orbital region of the prefrontal cortex (areas 12 and medial 11), while the portion of pars parvicellularis of the dorsomedial nucleus which lies adjacent to pars magnocellularis projects to the lateral half of the orbital region (areas lateral 11 and probably 47). The dorsolateral portion of pars parvicellularis is found degenerated after lesions of areas 45 and 46 in the inferior frontal gyrus, the ventrolateral portion after lesions affecting the vicinity of area 8 in the superior frontal gyrus. Degeneration of the central portion of pars parvicellularis seems to correlate with a lesion involving areas 46 and 9 (or 10) in the middle frontal gyrus. An anteroposterior axis in the dorsomedial nucleus tends to project to an anteroposterior axis in the frontal lobe.

These observations are not necessarily incompatible with Walker's concept of an axial correlation between the dorsomedial nucleus and the prefrontal cortex in monkeys ; but there are some disagreements in detail which necessitate further comparative studies.

(3) Degeneration in nucleus submedius of the thalamus is found to take place after leucotomy. It occurs after involvement of approximately the same areas as

those whose damage leads to degeneration in the adjacent ventrolateral portion of pars parvicellularis of the dorsomedial nucleus, i.e. the vicinity of area 8 in the superior frontal gyrus.

(4) The most anteromedial portion of the ventral nuclear complex of the thalamus projects to area 6, and not more rostrally. The anterior part of the reticular nucleus of the thalamus appears to share in this projection to area 6.

(5) The anterior thalamic radiation courses through the tip of the ventral nuclear complex. Thereafter the projection fibres from the medial parts of the dorsomedial nucleus run in the ventral half of the anterior limb of the internal capsule, while the fibres from the central and lateral parts of the dorsomedial nucleus, together with projection fibres from the anterior nuclear complex, run upwards into the dorsomedial half of the anterior limb of the internal capsule.

(6) The existence of a prefronto-pontile tract (Arnold's Bundle) in the human brain is confirmed. It is tentatively suggested that it arises in area 10. It passes down the medial aspect of the anterior limb of the internal capsule and terminates in dorsomedially situated cells of the anterior pons. The question of termination of elements of the tract in the subthalamic nucleus and substantia nigra is discussed.

(7) Preliminary investigation of long association tracts related to the prefrontal cortex reveals definite degeneration only in fibres which may represent the uncinate fasciculus and fasciculus cinguli. No degeneration is discernible in the subcallosal, superior longitudinal, arcuate or inferior occipito-frontal fasciculi. A sclerosed tract which runs for some distance adjacent to the lateral border of the subcallosal fasciculus is considered to represent part of the course of the projection fibres of the anteromedial nucleus of the thalamus to the cingular cortex, and perhaps also fronto-occipital long association fibres. (Authors' abstr.)

Disease of the Nervous System Occurring Among Research Workers on Swayback in Lambs.

(1) Four of the 7 individuals who worked intensively in their respective roles, on the demyelinating disease known as swayback in lambs, developed a disease of the central nervous system, which is clinically indistinguishable from disseminated sclerosis.

(2) This might be due to an hitherto unidentifiable occupational hazard of chemical research workers.

(3) This might also indicate that there is some causal connection between swayback and disseminated sclerosis, and some consideration has been given to speculation along these lines, viz. to some common infective agent acting only in the presence of a trace element deficiency.

(4) As swayback is a demyelinating disease and can be prevented by copper therapy, it is apparent that trace element deficiencies should be considered in connection with analogous diseases of man. (Authors' abstr.)

Some Physical Aspects of Encephalography.

Gas does not rise beyond the first constriction which it encounters when it is injected into a glass model of the ventricles.

Gas passes readily through the cavities when an element of elasticity is introduced into the closure of the model.

The flow of gas within glass models is analyzed and the findings correlated with encephalograph *in vivo*. It is believed that the lateral ventricles undergo expansion during encephalography. The expansion (and the entry of gas) depends upon the rise of the pressure at the distal end of the gas bubble caused by replacement of fluid in the lower midline cavities. The increment can be measured by the vertical extent of the column replaced. The expansion of the ventricles leads to expansion of the cerebral hemispheres, and downward displacement of cerebrospinal fluid from the subarachnoid space. The pressure differential expansion is greater when the head is erect. Hence the degree of expansion is greater when the head is erect than when it is flexed. This is the only means of entry of gas when the head is flexed sufficiently to bring the foramen of Monro below the termination of the aqueduct. When the head is erect, however, the elastic recoil of the cerebral hemispheres produces a downflow of fluid after each inflow of gas. This also contributes to the better filling in this posture.

The manipulations found necessary to transfer gas from one cavity of the model to another are described and the application of these findings to the radiography of the ventricles is considered. (Author's abstr.)

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The Effect of Oral Administration of Lactic Acid upon the Clinical Course of Depressive States.

The authors are well aware that the data offered in this paper are far from being complete and are by no means conclusive. Nevertheless, the results seem to indicate that the oral administration of lactic acid and sodium lactate influences the mood of patients in depressive states. In some instances the influence is no more than an improvement in sleep. In others, improvement in mood has occurred without any change in content of thought. In the patients who recovered from the depressive state under L.A., improvement in sleep, in mood and ultimately in content of thought became apparent. The authors do not wish to present this

method as a new or well-defined form of therapy of depressive states, but they feel that the evidence from this work seems to indicate that the oral administration of lactic acid and sodium lactate can exert some influence on the mood, suggesting that the role of carbohydrate metabolism associated with depressive states bears further investigation.

It is well known that almost all patients with depression ultimately recover. Might it not be, therefore, that what we have interpreted as improvement and recovery with L.A. is no more than what would be observed in the spontaneous course of the disease ? Their data seem to suggest, however, that when so many patients show improvement with the administration of this metabolite that this might not be mere coincidence. If the L.A. is withdrawn two or three days after the sleep has shown initial improvement, the patient usually returns to the disturbed sleep pattern, but sleep can frequently be restored again by renewed administration. This is the more striking as many of the authors' patients even with considerable doses of barbiturates or paraldehyde still had sleep disturbances. Another question might be raised as to the role of the diarrhoea associated with the ingestion of L.A. in effecting the improvement, but usually the patient experiences diarrhoea only during the first two or three administrations when his condition is still subjectively and objectively unchanged. In addition, diarrhea produced by purgatives has no effect on depressions. Changes of the acid-base balance or the effect of the intravenous administration of lactic acid were not studied. With regard to the role of suggestion, it must be reiterated that every attempt was made to preclude the use of psychotherapy, even in its subtle forms, and if suggestion were helpful in cases of depression, the introduction of convulsive therapy would have been unnecessary. Another objection might be that the authors' cases were only so slightly depressed that a short period of rest or the protection of a hospital environment might have served as reason for the improvement. This could be true in certain instances, although practically all of their patients were so deeply depressed that electic shock therapy had been recommended.

Work, physical exercise, " total push " and physiotherapy have long been regarded as adjuvants, if not sole remedies, in the cure of depressive states. Convulsive therapy might conceivably be looked upon as severe and concentrated muscular activity in which the stimulus to the central nervous system would be incidental only. If we now see that lactic acid given by mouth can produce effects similar to various physical therapies, we might well consider lactic acid as the common denominator in all these methods of treatment.

(Authors' abstr.)

Conditioned PGR (Psychogalvanic Response) in States of Pathological Anxiety.

The authors have endeavoured to investigate the effect of pathological anxiety on the rate of conditioning, in order to determine whether the rate of conditioning might be eventually a valuable objective indicator of the degree of anxiety. The conditioned stimulus was a nonsense-syllable of low association value, the unconditioned stimulus was the sound of a buzzer and the conditioned response was the PGR (psychogalvanic response).

Two groups were used in this experiment. One was a group of 82 Hunter College students and the other a group of 51 patients from the In-patient Department of the Payne Whitney Psychiatric Clinic, some of whom had anxiety and some of whom did not, according to psychiatric observation.

The criterion of conditioning for the test was three successive marked responses to the conditioned stimulus when unaccompanied by the sound of the buzzer. The score was determined by counting the number of times the buzzer was sounded before this criterion was fulfilled.

All but 4 of the normal group had a score of from 14 to 58, while with but one exception all of the patients who were diagnosed by the psychiatric staff as having anxiety had a score of 14 or less.

The repeat correlation on 36 of the normal subjects was ·88. On repeat tests given to the patients the score in most instances increased or decreased as their anxiety increased or decreased, according to psychiatric diagnosis.

Differences in age, sex and general intelligence did not appear to affect the rate of conditioning. (Authors' abstr.)

MAY,

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Neurotic Predisposition and the Disorganization Observed in Experiments with the Cambridge Cockpit.

It is contended that the disorganization of activity observed in the Cockpit test is essentially similar to that occurring in the neurotic reactions of aircrew to stress. In tests, the " overactivity " reaction resembled the acute anxiety reactions of aircrew, and the " withdrawal " reaction resembled various neurotic reactions, of which some have been labelled " hysteria." It has been shown that in some cases the effects observed in the tests were part of a more general reaction comprising frankly neurotic features. In some cases the test reaction recapitulated a previous neurotic illness. It has also been shown that the degree and type of the disorganization observed in the test depended upon the grade and type of the neurotic predisposition as assessed at an independent psychiatric interview. The test behaviour of experimental subjects, whether fit pilots, or pilots suffering from overt neurotic symptoms, tended to be of the kind expected. Thus the test behaviour was abnormal in two-thirds of the patients, but only in one-quarter of the fit pilots. The " overactivity " reaction was shown especially by those assessed as obsessional at interview, whereas the " withdrawal " reaction tended to be shown by those of hysterical disposition. (Authors' abstr.)

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Parenchymatous Cortical Cerebellar Atrophy Associated with Pick's Disease.

1. In a case of parenchymatous cortical cerebellar atrophy the loss of Purkinjë cells was combined with practically complete disappearance of nerve cells in the rostral three-fourths of the inferior olivary nucleus.

2. The atrophic changes in the cerebellum were associated with similar alterations in certain parts of the cerebrum where they were interpreted as those of Pick's disease.

3. Some features of the clinical history suggests that the condition was familial.

(Authors' abstr.)

On the Mechanism and Localization of the Symptoms of Electroshock and Electronarcosis.

The symptoms of electroshock and electronarcosis in decerebrate, uni- and bilateral decorticate preparations, and in animals with one deafferented hind leg were compared with the syndrome of shock and narcosis in normal animals.

In the decerebrate preparations shock and narcosis produced an enhancement of the decerebrate rigidity and an increase of the respiratory rate. It was postulated that in the normal animal these symptoms of medullar stimulation are masked by inhibition, produced by the stimulation of structures situated rostrally of the decerebration section in the midbrain.

The respiratory arrest observed in the course of electroshock and electronarcosis in the intact animal is considerably shortened in the decerebrate preparation. This indicates that the arrest in the normal animal is not caused by a paralyzing action of the current directly on the respiratory centre, but again by inhibition of that centre.

Uni- and bilateral decortication did not produce major changes in the symptoms of electroshock and electronarcosis. This may indicate the relative unimportance of the cortex for the production of these syndromes.

The observations on animals with one deafferented limb made it clear that in general no spinal reflex mechanism is involved in the production of the extensor contractions which are part of the shock and narcosis symptoms.

(Authors' abstr.)

Temporal Lobotomy.

A theoretical discussion is presented of the psycho-physiological mechanism of the prefrontal lobotomy and of the possible importance of the temporal lobes for emotional integration.

A new psychosurgical operation or temporal lobotomy is described by which a bilateral and deep section of the temporal lobe is produced in front of the tip of the temporal horn of the ventricle. The physiological aim of this operation is to cut the uncus, the beginning of the hippocampus, the uncinate fasciculus and other associational intercortical pathways.

The operation has been tried on two patients. One of them with predominant auditory hallucinations and strong associated emotional reactions, was not relieved by the temporal lobotomy. A secondary prefrontal lobotomy was more successful, although there were also more profound changes in the mental reactions after the frontal operation. In another case of a long-time deteriorated schizophrenic the temporal lobotomy was performed after an unsuccessful prefrontal operation. Some lessening of agitation was obtained. No gross neurological disturbances appeared after the temporal lobe sections and only in the first case was there some temporary difficulty in understanding speech and some loss of hearing. Further experience is necessary to evaluate fairly this operation, despite the fact that its first results have not been very striking. Larger sections of the temporal lobes may be necessary. (Author's abstr.)

J. NEUROPHYSIOL.

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*Effects of Potassium on the Endplate Potential and Neuromuscular Transmission in the Curarized Semitendinosus of the Frog. *Walker, S. M., and Laporte, Y.* 79

Synaptic Conduction to Giant Fibers of the Cockroach and the Action of Anticholinesterases.

1. A large number of sensory fibers from the cercus of the cockroach enter the 6th abdominal ganglion and form synaptic connections with 12 to 16 giant fibers which ascend the cord.

2. These synapses conduct synchronously up to 400 stimuli per second with a delay of 0·6 to 1·5 milliseconds. Spatial summation occurs.

3. Treatment with DFP causes marked synaptic facilitation alternating with periods of synaptic block, a condition which persists after washing in saline. The conduction process in the giant fibers appears to be unaffected by DFP in the concentrations used. It is concluded that trans-synaptic conduction is dependent on cholinesterase.

4. In the presence of DFP acetylcholine blocks trans-synaptic conduction, though alone it has no action.

5. Physostigmine, prostigmine and strychnine block trans-synaptic conduction with no sign of the facilitation and after-discharges characteristic of DFP. These drugs fail to sensitize the ganglion to the blocking action of acetylcholine.

(Authors' abstr.)

Generality of the Role of Acetylcholine in Nerve and Muscle Conduction.

Evidence suggesting the generality of an essential role of ACh in the conduction of nerve and muscle has been offered in two different types of experimental approach.

One method is based on the effect of cholinesterase inhibitors on the action potential of different kinds of nerves and of muscle.

1. As samples of sensory nerves, the optic and superficial ophthalmic nerves of *Raja erinacea* were selected. DFP abolishes reversibly the action potentials of sensory as well as of motor and mixed nerves.

2. The effect of cholinesterase inhibitors on adrenergic nerves was tested in experiments on the splanchnic nerve of *Rana catesbeiana*. Eserine abolishes the action potential of this nerve. The effect is easily reversible.

3. The action potential of the curarized frog's sartorius muscle (*Rana pipiens*) is completely and reversibly abolished by DFP. Eserine has the same effect.

Another type of approach, by which the assumption of an essential role of ACh may be supported, is evidence for the presence of the specific cholinesterase which is known to occur only in nerve and muscle.

4. In both sensory nerves in which the effect of DFP has been demonstrated, the optic and superficial ophthalmic nerve of *Raja*, specific cholinesterase is present in a concentration within the range that had previously been found in other nervous tissue and in muscle.

5. Cholinesterase is also found in high concentration in adrenergic nerves, i.e. the splanchnic nerve of the bullfrog and the postganglionic fiber of the superior cervical ganglion of cat. In the former the rate of ACh hydrolysis is 10 mg./g./hr. and in the latter it is 25 mg./g./hr.

6. In *Tubularia*, one of the hydrozoan coelenterates, which is the lowest group of animals to possess a nervous system comparable to that of higher animals, and in *Planaria*, the specificity of cholinesterase was found to be as high as that of any other cholinesterase tested.

(Authors' abstr.)

Giant Nerve Fiber System of the Crayfish. A Contribution to Comparative Physiology of Synapse.

The giant fibers in the central nervous system of the crayfish, *Cambarus clarkii*, were isolated in the oesophageal commissures and stimulated. It was found that the same peripheral mechanisms are brought into action by stimulation of any of the four giants.

The two medial giants are independent of each other. They conduct at a speed of 15–20 meters per second. They differ in no respect from peripheral nerve fibers.

The segmented lateral giants are interconnected in all ganglia posterior of the 4th thoracic. Stimulation of one invariably leads to excitation in the other. Their conduction speed is 10 to 15 meters per second. Transmission from one segment to the next of the same fiber is accomplished within 0·1 millisecond. The crossing time from one fiber to the other causes a similar delay in different ganglia, and takes about 0·5 millisecond. By cutting the lateral giants between different ganglia it is possible to delay the arrival of the impulse by forcing it to cross repeatedly.

In fresh preparations motor fibers of the roots of the abdominal ganglia are excited by stimulation of each of the four giants. The place of transfer between the lateral giant and the root at the same side is more peripheral than that with the medial giants.

The relation between impulses in the giants and the roots was studied. The first and third routes of the abdominal ganglia were found, in fresh preparations, to be excited by each giant impulse, no matter how closely they followed each other. With high frequencies of stimulation blocking of the root fiber occurs, preventing the passage of impulses. This blocking is not due to a refractory period, when the giant is stimulated with double shocks, the second impulse is effective under these conditions.

Aged preparations especially show a lengthening of the refractory period, in which a second giant fiber impulse does not cause a root potential.

Whereas the connections of the different elements in the lateral giants conduct with equal facility in either direction, the transmission from the giants to the roots is one-way. (Author's abstr.)

Topographical Representation of Muscles in Motor Cortex of Monkeys.

The topographical representation in the motor cortex of individual muscles acting over the ankle-joint has been investigated in nine macaque monkeys under Dial anesthesia. Simultaneous responses of eight muscles were recorded by isometric myographs during stimulation of the motor cortex.

The leg area was systematically explored millimeter by millimeter with a Goodwin thyratron stimulator and a unipolar electrode. The records were analyzed for evidence of muscle representation in terms of "solitary responses," tension-ratio and latency. Not only individual muscles, but also slips of a muscle have a focal point in the cortex from which a solitary response of that muscle is elicitable or the response is stronger and more prompt relative to other muscles. Among the muscles investigated, the anatomical flexors were found less responsive than the extensors. The inhibition of flexor responses by simultaneous excitation of the cortical extensor points is one factor in the unresponsiveness of the flexor muscles. Of the extensor group the muscles acting on the toes are more responsive than a muscle acting on the ankle. A hypothetical organization of Betz cells into a field composed of a focus and a fringe, the latter exhibiting overlap, is suggested to account for the type of muscle representation observed. (Authors' abstr.)

The Effect of Sedatives upon Delayed Response in Monkeys Following Removal of the Prefrontal Lobes.

Two monkeys which before operation gave a satisfactory performance in the delayed response experiment were unable to do so after removal of the prefrontal lobes.

Following intraperitoneal injections of nembutal or dial they were able to make scores reliably above chance up to delays of 25 seconds.

After withdrawal of drugs one animal retained this ability.

The significance of these results is discussed from the point of view that inattention due to increased activity and distractibility has been the cause of previously reported failure rather than the loss of immediate memory or retroactive inhibition. (Author's abstr.)

Effect of Di-isopropyl Fluorphosphate (DFP) on Action Potential and Cholinesterase of Nerve. II.

1. Studies on the correlation of the effects of DFP on the action potential and cholinesterase activity have been extended to the giant fibers of the stellar nerve of squid and to the fin nerve.

2. The effects of a range of concentration of DFP have been studied in these nerves and in the lobster cord.

3. The technique of the experiments has been modified to permit continuous recording of the action potential of the nerves during exposure to and recovery from the compound.

4. On exposure of the nerves to 1 mgm. of DFP at room temperature (22–25° C.) the action potential is abolished slowly. The action potential of the stellar nerve disappears in 10–12 minutes; that of the fin nerve in 30–40 minutes.

5. Higher concentrations of DFP result in quicker action. Three to four mgm. of DFP abolish the potential of the stellar nerve in 2–4 minutes. Five mgm. of DFP act on the giant fibers of the lobster cord in the same time.

6. The reappearance of the spike during recovery from exposure to the higher concentration is more rapid than when lower concentrations of DFP have been used. The spikes reappear within a few seconds and recovery is complete within a few minutes.

7. Tested under the same conditions, the action of eserine on the stellar nerve is slower. The molar concentration of eserine must be about twice as high as that of DFP to obtain the same rate of action. This indicates a lower rate of penetration of eserine.

8. After the electrical activity of the nerves of the three preparations had returned to normal, the cholinesterase activity was determined. In all cases the enzyme activity was about 20 per cent. of untreated control nerves.

9. In similar experiments performed on the abdominal cord of the lobster, but at 5–7° C., the remaining enzyme activity was close to 50 per cent. as was to be expected from the lower rate of the irreversible inhibitory process at low temperatures.

10. The correlation established between the presence of cholinesterase and the electrical activity of the nerves of the squid and lobster has been extended to the case of the bullfrog and frog sciatic nerves. Two hours after injection of massive doses of DFP into the animals, cholinesterase was still present in the nerves.

11. The presence of the cholinesterase was demonstrated by the method of bio-assay. It is shown that the manometric technique is not adequate in this particular case, due to a combination of adverse factors. (Authors' abstr.)

Effects of Potassium on the Endplate Potential and Neuromuscular Transmission in the Curarized Semitendinosus of the Frog.

1. A technique for intra-arterial injection in the isolated muscle is described.

2. Small increases of K first facilitate and then depress neuromuscular transmission. It is suggested that both of these effects of K may involve alteration of the excitability of the muscle fibers and alteration of the size of the e.p.p.

3. During the period of depression a response is followed by prolonged reduction of responsiveness. It is pointed out that K diminishes restoration in some manner not revealed by the electrical signs of repolarization. (Authors' abstr.)

MARCH.

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*Effect of DFP on Action Potential and Cholinesterase of Nerve. III. *Grundfert, H., et al.* 155

Decerebrate Rigidity.

It is known that intravenous injection of appropriate doses of sodium cyanide results in a transient state of true decerebrate rigidity. The present experiments show that during the period of functional decerebration the electrical activity of all structures above the midbrain is absent. The activity of the suppressor region in the bulbar reticular formation is slightly depressed, while that of the facilitatory region in the lateral pontile tegmentum is unchanged or increased.

The hypothesis is advanced that both NaCN and appropriate lesions in the midbrain produce decerebrate rigidity by interrupting all afferent impulses to the bulbar suppressor region, thereby causing a deprivation-paralysis of that structure. The facilitatory region in the lateral pontile tegmentum, however, continues to receive afferent impulses from the cranial nerve nuclei as well as from the cord, and thus its facilitatory influence on the internuncial pools of the ventral horns of the cord continues unchecked. The balance between inhibitory and facilitatory impulses arriving in the cord is thereby upset. In the absence of impulses from the suppressor region in the bulb, this internuncial activity is greatly increased and is manifested peripherally as extensor rigidity.

It has been shown that the decerebrate state induced by NaCN may be modified by small lesions in the reticular formation of the brain stem and, furthermore, that it may be entirely prevented by lesions which selectively destroy the facilitatory region in the pontile tegmentum. Lesions restricted to the midline suppressor region, on the other hand, yield decerebrate rigidity. Although this hypothesis cannot be proven by the facts available at present, it seems to explain all the known observations regarding decerebrate rigidity. (Author's abstr.)

Convulsive Activity Induced by Fluoroacetate.

(1) Intravenous injection of sodium fluoroacetate causes local, rhythmic, seizure discharges in subcortical structures. These occur at the time when the animal is exhibiting repeated tonic seizures.

(2) There is no clear correlation between the electrical activity of the cortex and the paroxysmal activity occurring in the thalamus, hypothalamus or reticular formation of the pons.

(3) Dome and spike activity has been recorded from the cortex synchronously with rapid seizure discharges in subcortical structures. (Author's abstr.)

Injury Potentials Along Peripheral Nerves in Relation to Histological Structure.

The injury potentials at different levels of peripheral nerves in the cat's lumbosacral region have been measured. They were found to diminish continuously from the spinal nerve roots towards the periphery. The proportion between the injury potentials of the ventral roots and the tibial nerve was 4 : 1. Ventral roots had, on an average, 4·7 mV higher injury potentials than dorsal roots.

This drop of the injury potential along the nerve was found to be related to the calibre of the nerve fibres at the different levels. A general correlation was observed between cross-sectional fibre area per total nerve cross-sectional area on the one hand and injury potential on the other, so that a greater relative fibre cross-sectional area corresponded to a higher injury potential.

Calibre spectra are presented for a number of nerves at different levels as well as for motor and sensory roots (cat). (Author's abstr.)

Injury Potentials at Different Levels of Cross-section of Spinal Cord.

The injury potentials of different points of the cross-section of the spinal cord have been investigated with wick electrodes or glass capillaries and compared with the histological picture.

The grey substance always has a lower injury potential than the white substance.

The white substance of the dorsal funiculus has a higher injury potential than that of both lateral and ventral funiculi.

The value of the injury potential of the dorsal funiculus was found to be 28·5 mV ± 2·1 (17 exp.), measured against the surface of the cord. (Author's abstr.)

Effect of Afferent Impulses on Cortical Suppressor Areas.

Afferent nociceptive impulses initiated by electrical or mechanical stimulation of the sciatic nerve, injection of hypertonic NaCl solution into a muscle, or stretching of a contractured muscle led to an excitation of the suppressor as well as the sensori-motor and projection areas of the cortex. Quantitative experiments show similar reactions to threshold and supra-threshold stimuli. The excitatory process seems to be based on a diminished synchronization and on recruitment of additional cortical neurons. It is suggested that the suppressor areas are involved in a homeostatic mechanism. (Author's abstr.)

Influence of Suppressor Areas on Afferent Impulses.

Electrical stimulation of the frontal, parietal, or occipital suppressor areas of the cat results not only in a diminution or suppression of cortical activity, but also in a diminution or suppression of the cortical effects induced by afferent somatic and visceral impulses. (Author's abstr.)

Prolonged Facilitation of Synaptic Excitation in Sympathetic Ganglia.

Following the conduction of one or more volleys of impulses along the presynaptic and postsynaptic neurones of a sympathetic ganglion, there are long-lasting changes which facilitate subsequent excitation of the ganglion cells by impulses in the presynaptic fibers. Such facilitation may persist for many minutes.

A single ganglion cell which does not respond to slowly recurring volleys of preganglionic impulses may be brought into action by the arrival of more frequently repeated volleys. Presumably this is due to the persistance of some effect induced by each presynaptic impulse. The frequency of discharge from a cell is increased by an increase in the frequency of excitation.

When studying the response of a group of ganglion cells, the magnitude of the postganglionic action potential provides a measure of the number of ganglion cells responding to a volley of preganglionic impulses. The magnitude of this postganglionic response to a given preganglionic volley may be increased by as much as 10-fold, following a brief period of repetitive excitation through the preganglionic fibers. This indicates that many more ganglion cells respond to a given number of presynaptic impulses, following previous activity.

By increasing the frequency and duration of the conditioning train of impulses, the number of ganglion cells responding to a given preganglionic volley and the duration of this facilitation are increased. Following a single conditioning volley, a small degree of facilitation is detectable for a few seconds. After many volleys, the effect may last for more than five minutes.

Antidromic stimulation does not facilitate the response of a ganglion cell to synaptic excitation; on the contrary, it lowers the irritability of the cell. Also, the excitation of a ganglion cell by one set of presynaptic endings does not increase the irritability of the cell for subsequent excitation by other presynaptic endings. Furthermore, the response of a cell to acetylcholine is reduced by previous synaptic or antidromic excitation. These facts argue against the possibility that prolonged facilitation is due to previous activity of the ganglion cell itself.

The duration and magnitude of the prolonged facilitation is unaffected by modifying the circulation through a ganglion. This and other evidence indicate that the effect is not due to the persistence of some chemical agent in the synaptic region.

There remains the possibility that prolonged facilitation is due to a long-continued alteration in the presynaptic endings, which causes the nerve impulses arriving at the synapse to have a more effective excitatory action.

The relation of these phenomena to our recent observation of prolonged after-discharge of rhythmically recurring impulses is discussed. (Authors' abstr.)

Effect of Di-isopropylfluorophosphate (DFP) on Action Potential and Cholinesterase of Nerve. III.

The study of the correlation between conduction and cholinesterase activity in nerves exposed to DFP has been continued and additional proof is offered for the close association of the two processes. The following results have been obtained with the superior cervical sympathetic nerve of the cat at 37° C.

1. When the nerve is exposed to 4 mgm. of DFP per c.c. (0·02 M), the action potential is abolished within 2–5 minutes, but recovers when the nerve is returned to Ringer's solution.

2. A, B, and C fibers are equally affected.

3. After recovery the cholinesterase activity is about 20 per cent. of the normal. This is the same percentage as found previously in other nerves treated with DFP in the same way.

4. On additional exposure of the nerve to DFP for 20 minutes, the action potential is abolished irreversibly. This rate of irreversible abolition of the action potential is in good agreement with the rate of irreversible inactivation of cholinesterase exposed *in vitro* to DFP at 37° C.

5. Eserine at an equimolar concentration abolishes the action potential in the same way, although at a lower rate.

6. In contrast to the effect of DFP, the action of eserine is reversible even if the nerve is exposed for an additional 20 minutes after abolition of the action potential. This is in agreement with the reversibility of the cholinesterase inhibition by eserine demonstrated on the same nerves.

With the bullfrog sciatic nerve at room temperatures (20-24° C.), the following results have been obtained:

7. The action potential is reversibly abolished by exposure of the nerve to eserine (6·5 mgm. per c.c. or 0·02 M).

8. Even when the nerve is exposed to eserine repeatedly and for long periods of time, the action potential reappears when the nerve is washed in Ringer's solution.

9. On exposure of the nerve to 4 mgm. of DFP per c.c. for 27–85 minutes, the action potential was abolished but recovered when the nerve was returned to Ringer's solution. Exposure for 120 minutes, however, abolished the action potential irreversibly. The time required to abolish conduction irreversibly is about the same as that found with the lobster cord at the same temperatures.

10. The parallelism between cholinesterase activity and action potential found previously in nerves exposed to DFP as a function of time has now also been established as a function of temperature. (Authors' abstr.)

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J. PSYCHOL.

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Psychological Factors in Susceptibility to Motion Sickness. *Zwerling, I.* . 219
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The Efficiency of the Group Rorschach Test in the Psychiatric Screening of Marine Corps Recruits.

The use of the Group Rorschach Test, in conjunction with a mental test and a pencil and paper personality inventory, in the psychiatric screening of Marine Corps recruits has been described. It has been shown that in the author's experiment the Group Rorschach Test differentiates between recruits who adjust and those who fail to adjust to recruit training in the Marine Corps. The group method had been shown to identify neuropsychiatric misfits missed by a typical pencil and paper personality inventory and that a simple and economical inspection evaluation of each group protocol is adequate to the needs of psychiatric screening of recruits. The Mean-Square contingency coefficient between inspection evaluations of 99 group records by two clinical psychologists is ·80, and the Mean-Square contingency coefficient between inspection evaluations of 141 group protocols and a check list evaluation of the same group records after they had been scored is ·91.

The experiment has shown that there is a high positive relationship between inspection evaluated group records and Drill Instructor performance ratings of the same subjects. There is also a high positive relationship between inspection evaluated group protocols and the personal and social history factors of the same subjects. It has also been suggested that the Group Rorschach Test is practicable for use in the psychiatric screening of Marine Corps recruits and leads to the identification of over 86 per cent. of those neuropsychiatrically unfit, when combined in a test battery with a psychometric test and a pencil and paper personality inventory.

(Author's abstr.)

J. SOC. PSYCHOL.

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*Correlates of Criminal Behavior. *Lodge, C. T.* 3
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Ibid. The Stupid Drinker. *Hampton, P. J.* 119

Correlates of Criminal Behavior.

The study here reported has attempted to demonstrate the applicability of the bisected variable tetrachoric method as an instrument for research in a part of the confusing domain of criminology. The results that have been obtained have convinced the writer, at least, that such an approach has great potential value.

It seemed at the outset that simply to establish an intercorrelation table between the various traits might shed light on the problem of linkage among the forces

producing psycho-social conflict and resulting in arrests for criminal behaviour. In a sense this belief has been supported by the findings. But in another sense we have succeeded in raising more new questions than we have been able to answer old ones. Further development of the present data should provide results of even more interest than those already suggested. Such development might advantageously consist of reorganization or grouping of the variables so that those showing congruent profiles are juxtaposed. This will not only effect a more logical arrangement in that related items will be brought together, but it will also facilitate interpretation by rendering smoother and more easily read correlation profiles.

It is not unreasonable to surmise that a factor analysis of all or part of the set of variables might help greatly to reduce some of the complexities that are now present in the statistical raw data, i.e. the correlation table. It is evident from the fashion in which the profiles tend to form clusters that many of them are operationally very similar to each other. Discovery of what Tyron calls " operational unities "—general components which act as if they were unitary determiners of nominally different characteristics—should tend greatly to simplify the problems connected with our large table by reducing the number of " factors " with which we have to deal. There is, for instance, clearly some unitary determiner which causes the correlations for the four mental tests, school achievement, and diagnosis of intelligence defect all to act in a similar fashion in relation to all of the other variables in the table. " Estimated poor risk " and " prison sentences " and possibly other traits also can be combined into a single operational unity for purposes of further simplification.

Our method of inquiry has plainly indicated one profound generalization. This is that criminality is not an isolated phenomenon, but that it is inextricably a part of the total social organism. Symptom treatment of the type now prevalent—punitive imprisonment, legislative verbiage, increased police forces, etc., can of themselves accomplish no fundamental cures for " Crime." This can arise only from far-reaching adjustments of our entire social structure. If the present attempt serves only to demonstrate in some small measure a few of the many influences that contribute to the uniqueness and individuality of every criminal, and if it thereby serves to modify some of the stereotypes which obscure our thinking in regard to criminal behaviour, it will not have been without justification.

(Author's abstr.)

MED. J. AUSTR.

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*The Significance of F. A. Carus and G. H. v. Schubert for the Psychology of the Dream. *Bossard, R.* 281
*Self-observations During Mescaline Intoxication. *Fischer, R.* . . . 308

The Significance of F. A. Carus and G. H. v. Schubert for the Psychology of the Dream.

The usual claim that we owe the first decisive step towards an analysis of dreams to Freud is unjustified. It undervaluates the contributions of the philosophers Carus and Schubert, who lived about 100 or 75 years respectively before Freud. These men recognized, among other things, the symbolism of dreams and their relations to mythology and poetry. K. F. MUENZINGER (Psychol. Abstr.).

Self-observations During Mescaline Intoxication.

The effects of 0·6 gm. of mescaline are described. Color hallucinations were observed similar to those described by other authors. The state of euphoria, which lasted a few hours, gave way to a psychosis of 6–7 hours' duration, characterized by intensified suggestibility and fears of death.

K. F. MUENZINGER (Psychol. Abstr.).

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1. Psychiatry.

Rehabilitation of British Industry's Neurosis Cases. [*J. Rehabilit.*, **12**, *No.* 4, 33–5, 35, (1946).]

The first Industrial Rehabilitation Center established in England in 1943 in one year treated satisfactorily 580 men and 460 women, many of whom were medically and psychiatrically difficult, usually because of occupational and social maladjustment. Each patient received psychiatric interviews with intelligence and aptitude tests. Workshops and daily physical training were provided, with communal activities every evening. A 2-week training course for 30 trainees is to be established for industrial medical and lay workers, sponsored by 150 industrial firms. A research department is being planned to investigate the causes of breakdowns in industry. F. A. Cooksley (Psychol. Abstr.).

Schizophrenia in Children. [*Ohio St. med. J.*, **42**, 1248–54 (1946).]

The author presents 7 cases of schizophrenia in children. The symptoms by which schizophrenia in children may be diagnosed when other disorders are ruled out are : Seclusiveness associated with irritability if seclusive activities are interfered with ; excessive day-dreaming ; bizarre behavior ; diminution of interests and preoccupation with interests common to younger children ; sensitivity to criticism, often associated with violent outbursts ; and a reduction in physical activity. Prognosis in the 7 cases cited does not appear too favorable. Recent reports, however, indicate that up to 50 per cent. of schizophrenic children may show improvement. Treatment is primarily aimed at helping these children to improve their personal and social relationships. The treatment can best be carried out in a hospital-school-institutional setting. F. C. Sumner (Psychol. Abstr.).

Psychogenic or Hypothalamic Amenorrhea. [*Med. Clin. N. Amer.*, **30**, 1103–14 (1946).]

Because of psychologic disturbances the hypothalamus may through loss of normal nerve impulses fail to release luteinizing hormones from the anterior pituitary gland which are necessary for the production of estradiol. A non-estrogenic hormone may then inhibit the follicle stimulating hormone required for menstruation. Diagnosis is made by ruling out physical causes and by discovery of an earlier psychic shock. As emotional stress is eliminated, the condition may disappear. Other cases may require psychoanalysis, with reassurance that there is no organic disease. The woman who is maladjusted, perhaps unconsciously, is more difficult to treat. The theory that release of luteinizing hormones from the anterior pituitary system is affected by nervous stimuli from the hypothalamic-pituitary nervous system has been experimentally proved.

F. A. Cooksley (Psychol. Abstr.).

2. Biochemistry, Physiology, Pathology.

Retromammillary Inhibition of Cortically Induced Movement. [*Proc. Soc. exp. Biol., N.Y.*, **63**, 76–8 (1946).]

The authors discovered a rostral midbrain area in the cat which, when stimulated while cortically-induced movement was in progress, inhibited these movements. Although the same areas in monkeys were similarly studied, no inhibitory responses were observed. C. P. Stone (Psychol. Abstr.).

Identification of the Substances which Produce a Positive Wassermann Test in the Cerebrospinal Fluid. Lipides with Antigen Properties. Prunell, Alfredo (Hospital Vilardebo, Montevideo). [*Arch. soc. biol. Montevideo*, **13**, 33–65 (1946) (*English and French summaries*).]

The luetic antibody is obtained from the cerebrospinal fluid (I) of luetic patients by the following modification of the Takata reaction : Incubate at 37° for 15–20 minutes the mixture of 3 c.c. (I) with 0·30 c.c. of a mixture (II) of 5·6 c.c. M/15 KH_2PO_4 and 94·4 c.c. of M/15 Na_2HPO_4, and with 0·30 c.c. 0·5 per cent. $HgCl_2$. Cool, centrifuge, and decant. Treat the precipitate thrice with 10 c.c. water and

5 minutes' centrifuging. Add 3 c.c. 0·85 per cent. physiological salt solution to the precipitate, bring to pH 6 with 0·01 N HCl and warm to 40° until completely dissolved. Add (II), diluted to one third, until pH 6·7. The antibody is precipitated at pH 7·4. By fractional precipitation with $(NH_4)_2SO_4$ it is shown to consist of a euglobulin and a pseudoglobulin. The isoelectric point of the reagin is 5·8. The results of the Wassermann, Lange, and Kahn reactions are the same with these globulins as with the original luetic (I). Only 0·0004 gm. of the incompletely purified globulin-antibody (III) give a positive Wassermann test. (III) shows colloidal properties in dialysis. No substance with a bearing on the method of complement fixation appears in the dialyzate. The lipides extracted from luetic (I) have antigenic properties like those extracted from heart muscle. Procedure for preparation: Evaporate 12 c.c. centrifuged luetic (I) at 37°, add 6 c.c. absolute EtOH, stir for 30 minutes, incubate at 37° for 24 hours, centrifuge and evaporate by an air current. To the residue add a few drops of water and 3 c.c. 0·85 per cent. physiological salt solution. This emulsion effects a positive Wassermann test of the same intensity as a solution of 1 per cent. Bordet antigen.

F. Fromm (Chem. Abstr.).

Magnesium in Normal and Pathologic Cerebrospinal Fluid. Castells, C., and Gherardi, J. [*Arch. soc. biol. Montevideo*, **13**, 23–5 (1946).]

In the cerebrospinal fluid of 6 normal persons 1·40–3·6 mgm. per cent. Mg were found by Youngberg's modification of Denis's method (*C. A.*, **25**, 1857). In 9 cases of epilepsy, tabes, dementia precox, hydrocephalus, and manic-depressive psychosis the same Mg level was found. F. Fromm (Chem. Abstr.).

Lysozymic Activity of Human Cerebrospinal Fluid. Caselli, Patrio, and Tolone, Salvatore (*Univ. Naples, Italy*). [*Boll. soc. ital. biol. sper.*, **22**, 539–40 (1946).]

Normal human cerebrospinal fluid was dialyzed to destroy the inhibiting activity and was then shown to exert lytic activity against *Micrococcus lysodeikticus*. Some pathological fluids manifested this activity without dialysis.

Helen Lee Gruehl (Chem. Abstr.).

Antilysozymic Activity of Human Cerebrospinal Fluid. Caselli, Patrio, and Tolone, Salvatore (*Univ. Naples, Italy*). [*Boll. soc. ital. biol. sper.*, **22**, 537–9 (1946).]

The antilysozymic activity of the fluid was tested against normal ovalbumin and normal blood serum. Normal cerebrospinal fluids exerted a marked inhibitory effect on the lysozymic activity of these substances. Pathological fluids with a moderate protein content exerted a definite but less marked inhibiting effect. This activity was thermostable and was reduced by lowering the pH to the acid range. It disappeared on dialysis. Helen Lee Gruehl (Chem. Abstr.).

Relation Between the Chemical Composition of Spinal Fluid and the Course of Birth. Makar'ev, F. A. [*Akusherstvo i Ginekol., No.* 3, 54–5 (1946).]

Rapidly progressing course of birth is characterized by a high K-ion level in the spinal fluid and a lower level of Ca and Mg. which characterizes a higher tone of the sympathetic centers. The process of slow birth is accompanied by low K level, and higher levels of Ca and Mg. G. M. Kosolapoff (Chem. Abstr.).

Convulsions Produced by Fetal Anoxia: Experimental Study. Fender, Frederick A., Neff, William B., and Binger, Grace (*Standford Univ. School of Med., San Francisco*). [*Anesthesiology*, **7**, 10–13 (1946).]

Nervous tissue is more sensitive to O deprivation than any other type of body tissue. This tends to be most marked at the highest neurologic levels. Cases are reported of 2 pups born of mothers which had been deprived of normal O supply shortly before delivery. Both pups developed a convulsive state, one five and one six weeks after birth. It is felt that anoxia played a role in the development of this state. It is further believed that fetal and neonatal anoxia in human beings may play a major part in the development of epilepsy.

Ruth Berggren (Chem. Abstr.).

The Production of Electricity by Nerve. [*Science*, **104**, 569–70 (1946).]

Results from experiments on the effect of biological substances on the "oil-cell" model of the nerve impulse are discussed as evidence supporting the theory that the electrical nerve impusle is a phase-boundary potential produced by acetylcholine in contact with nerve lipoid. F. A. Mote (Psychol. Abstr.).

Effect of Hyperventilation on Carotid Sinus Reflexes and Tone of the Vasomotor Center. Heymans, C., Pannier, R., and van Ostende, A. (Univ. Gand, Belgium). [*Arch. intern. pharmacodynamie*, **72**, 430–9 (1946).]

Hyperventilation, alkalosis and acapnia in dogs cause no fall in blood pressure, nor do they depress the reflexes from the carotid sinus or the central vasoconstrictor tone. M. L. C. Bernheim (Chem. Abstr.).

Indophenol Oxidase of the Central Nervous System. III. Indophenol Oxidase of Various Portions of the Nerves of the Human Fetus. Pesce, Vito Stefano (Univ. Bari, Italy). [*Boll. soc. ital. biol. sper.*, **22**, 646–7 (1946); *cf. C. A.*, **41**, 491f.]

The indophenol oxidase activity was lacking in the human fetal nervous system up to the 5th month of development. After that period it was present in varying degrees in the different portions of the nervous system. It was present in greater amounts in the gray than in the white matter.

Helen Lee Gruehl (Chem. Abstr.).

Indophenoloxidase of the Central Nervous System. IV. Action of Biogenic Amines on the Indophenoloxidase Activity of the Nervous System. Mitolo, Michele. [*Biol. ital. biol. sper.*, **22**, 651–4 (1946); *cf. C. A.*, **41**, 1302i.]

Experiments on chickens, guinea-pigs, rabbits, rats and dogs showed that the injection of biogenic amines in intoxicating but sublethal doses caused a diminution in the indophenol oxidase activity of the nervous system. This diminution was very marked with adrenaline and less marked but definite with histamine, triethanolamine and the other amines studied.

V. Action of Barbiturates on the Indophenoloxidase Activity of the Nervous System. Ruccia, Domenico. [*Ibid.*, 654–6.]

Barbiturates, administered in high doses to rats and rabbits, induced a definite diminution in the indophenoloxidase power of the nervous system.

Helen Lee Gruehl (Chem. Abstr.).

Diphasic Action of Chemical Mediators of Nervous Impulse. Peruzzi, Pietro (Univ. Pisa, Italy). [*Boll. soc. ital. biol. sper.*, **22**, 426–7 (1946).]

In perfusion experiments on isolated guinea-pig heart, adrenaline in a concentration of 10^{-11} sometimes exerts a stimulating action, sometimes has no effect, and sometimes exerts an inhibiting effect. Acetylcholine exerts a stimulating action in a concentration of 10^{-7} and an inhibiting effect in a concentration of 10^{-6}.

Helen Lee Gruehl (Chem. Abstr.).

Chemical Mediators in the Sympathetic Nervous System. West, G. B. [*Pharm. J.*, **158**, 6–7 (1947).]

A discussion of sympathin I and sympathin E and their relationship to adrenaline and noradrenaline. H. M. Burlage (Chem. Abstr.).

New Problems of Muscle and Nerve Physiology. von Muralt, Alexander (Hallerianum, Bern, Switz.). [*Arztl. Monatsh. (Schwarzenberg, Switz.)*, **2**, 923–34 (1946).]

A review in which the relationships between chain reactions and muscular activity are discussed, as well as the electric and chemical viewpoints in nerve physiology. J. M. Little (Chem. Abstr.).

Disturbances of Neuromuscular Excitability During Alimentary Imbalance and Avitaminoses. XII. Application of Chronaximetric Methods to the Study of Members of the Vitamin B Complex in the Rat. Lecoq, Raoul, Chauchard, Paul, and Mazoue, Henriette (Sorbonne, Paris). [*Bull. soc. chim. biol.*, **28**, 305–14 (1946); *cf. C. A.*, **40**, 6129[8].]

XIII. Correction of the Disturbances of Chronaxia in B Complex Avitaminosis in the Pigeon and Its Relation to Dietary Balance. [*Ibid.*, 314–22; *cf. C. A.*, **40**, 3804[4], 5116[5].]

XIV. Role of the Principal Vitamins in the Maintenance of the Acid-base Balance of the Body. [*Ibid.*, 595–600.]

Discussion based on 8 previous papers. Vitamins C and D have an anti-alkalosic action; A, E and the B complex are antiacidosic. Carotene has no action in either direction (in rats).

XV. Avitaminoses A, C, D and E in the Pigeon. [*Ibid.*, 601–7.]

By chronaximetric methods it was shown that avitaminoses A and E result in chronic acidosis with some polyneuritic symptoms and that avitaminoses C and D cause symptoms of alkalosis. L. E. Gilson (Chem. Abstr.).

The Production of Experimental Pellagra by Adenine. Raska, Sigwin B. (*Cornell Univ. Med. School, New York, N.Y.*). [*Science*, **105**, 126–7 (1947).]

The physiological effects followed by death of one series of dogs which had included in their diet 400–500 mgm. adenine or free base mixed with $NaH_2PO_4.H_2O$ and of another group which were fed 300 mgm. adenine daily are described. These experiments show a direct relationship between purine metabolism and avitaminosis of which pellagra is the most frequent variety. Adenine probably combines with the constituents of vitamins or their precursors preventing their utilization, for many symptoms observed are those found in cases of extreme vitamin deficiency.
H. B. Klevens (Chem. Abstr.).

Observations on Pellagra in American Prisoners of War in the Philippines. Lewis, Charles F., and Musselman, Merle M. (*Univ. Hospital, Ann Arbor, Mich.*). [*J. Nutrition*, **32**, 549–58 (1946).]

Pellagra was observed in American troops living for 3 years on a deficient diet in Japanese prison camps in the Philippine Islands. Men developed pellagra while on a diet low in calories, high in carbohydrates, and lacking in animal proteins, fresh fruits and vegetables. It appeared in epidemic proportions after 6 months on a deficient diet. The signs and symptoms that were observed are described. The clear separation of certain dermal and neurological lesions according to specific vitamin lack was difficult. Processed foods, a crude yeast culture, and pure vitamin preparations were effective in controlling pellagra. Pure vitamin preparations were more effective when the diet was more adequate.
W. B. Esselen, jun. (Chem. Abstr.).

Histamine Contents of Various Nerves During Excitation. Ryvkina, D. E., and Bulatova, N. N. (*Inst. Evolut. Morphol., Acad. Sci., Moscow*). [*Byull. Eksptl. Biol. Med.*, **22**, *No.* 9, 32–5 (1946).]

In the animal species studied the histamine contents of the nerves decreased in the order: Phrenic, vagus and sciatic. In rodents (rats and rabbits) the nerve histamine concentration is greater than in cats and dogs. The irritation of nerves by an electric current of threshold strength leads to an increase in histamine concentration. Stronger currents lead to a histamine depletion. The histamine concentration remains unchanged during morphine narcosis whether threshold or stronger currents are used. H. A. Wegner (Chem. Abstr.).

Reciprocal Action Between Thiamine, Acetylcholine and Cholinesterase. Knipst, I. N. (*M. V. Lomonosov Univ., Moscow*). [*Byull. Eksptl. Biol. Med.*, **21**, *No.* 3, 19–20 (1946).]

The experiments were carried out in two series. In the first series the response of the rectus muscle of a frog's abdomen to acetylcholine alone and with thiamine

was studied. The muscle was divided into two parts. On one part progressive concentrations of acetylcholine were used, on the other the same concentrations of acetylcholine with the addition of several concentrations of thiamine. The highest concentrations of thiamine depressed the response of the muscle to acetylcholine, the lowest concentrations stimulated it, and the middle concentrations depressed it in some cases and stimulated it in others. In the second series the response of the same muscle to cholinesterase was studied. The addition of thiamine to this esterase always inhibited its hydrolyzing action on acetylcholine, the degree of inhibition depending on the concentration of thiamine and on the fact whether true or pseudocholinesterase was used. J. DAVIDSON (Chem. Abstr.).

Titrimetric Determination of the Cholinesterase Activity of Blood. Scoz, G., and Michele, G. De (Univ. Naples). [*Boll. soc. ital. biol. sper.*, **19**, 7–8 (1944).]

Add 0·1 c.c. of whole blood to 3 c.c. of dilute Na barbital buffer of pH 8. Place in a thermostat at 40° for 10 minutes, then add 1 c.c. of a solution containing approximately 33 mgm. of acetylcholine chloride. Incubate 3 hours at 40° and titrate to pH 8 with 0·02 N NaOH. A blank determination without blood must be made to determine how much acetylcholine is hydrolyzed by the buffer solution during incubation. L. E. GILSON (Chem. Abstr.).

Nerve Conduction after Inactivation of Cholinesterase. Boyarsky, L. L., Tobias, Julian M., and Gerard, R. W. (Univ. of Chicago). [*Proc. Soc. Exptl. Biol. Med.*, **64**, 106–8 (1947).]

Frog sciatic nerve, exposed to diisopropyl fluorophosphate in a suitable concentration in peanut oil and for a time sufficient to inactivate its cholinesterase, can still conduct impulses with entirely normal action potentials. Cholinesterase is not essential for nerve conduction. L. E. GILSON (Chem. Abstr.).

Acetylcholine Formation in B_1 Avitaminosis in Man. Anosov, N. N. [*Byull. Eksptl. Biol. Med.*, **21**, *No.* 3, 16–19 (1946).]

Acetylcholine formation was tested by the action of the blood from avitaminosis B_1 patients on isolated organs. Arterial blood taken 30 minutes after administration of 2 mgm. of eserine was placed in a test tube containing enough eserine to make a concentration of 1 : 100,000, and was tested on the eserinized abdominal muscle of a frog and small intestines of a mouse and cat. Observations were made on 4 patients with mild, and 18 patients with acute, avitaminosis. In no case did the blood of the patients show any acetylcholine action. The parenteral administration of eserine caused an accumulation of acetylcholine in the blood and also caused the restoration of the functions and mechanisms, especially the sensitivity and functions of the vegetative nervous system, which were disturbed by the depressed formation of acetylcholine in the blood. J. DAVIDSON (Chem. Abstr.).

Effect of Organ Extracts and Their Fractions on Acetylcholine Synthesis. Torda, Clara, and Wolff, Harold G. (Cornell Univ. Med. Coll., New York, N.Y.). [*Am. J. Physiol.*, **148**, 417–23 (1947).]

The results indicate that blood serum and animal tissues contain substances that increase acetylcholine synthesis and also decrease it. Human blood serum and water extracts of various animal tissues contain substances that increase acetylcholine synthesis. These substances are in part nondialyzable (proteins, lipoproteins) and in part dialyzable, many of them heat-stable and organic. Ether extracts of serum and various tissues contain factors that decrease acetylcholine synthesis. For some of the depressor effects fatty acids are responsible.
E. D. WALTER (Chem. Abstr.).

Anaerobic Synthesis of Acetylcholine. Lipton, M. A., and Guzman Barron, E. S. (Univ. of Chicago). [*J. Biol. Chem.*, **166**, 367–80 (1946).]

The brain enzyme which synthesizes acetylcholine anaerobically is soluble and can be extracted from acetone-dried preparations. Citrate, *cis*-aconitate, or acetoacetate must be present, and probably yield an " active " acetate, which acetylates choline. Adenosine triphosphate, K, and a coenzyme from boiled yeast or animal tissues are also necessary for the synthesis. M. L. C. BERNHEIM (Chem. Abstr.).

Action of Histamine, Acetylcholine and Peptone on the Sympathectomized Dog. Bennati, D., and Bacq, Z. M. (Inst. Physiology, Montevideo, Uruguay). [*Arch. intern. pharmacodynamie*, **72**, 397–404 (1946).]

Sympathectomized and vagatomized dogs are more sensitive to small doses of acetylcholine and histamine than vagotomized dogs with enervated carotid sinus. Sympathectomized dogs do not recover completely from peptone shock.

M. L. C. Bernheim (Chem. Abstr.).

Presence of Choline Acetylase in Striated and Cardiac Muscle. Nachmansohn, David, Berman, M., and Weiss, Michael S. (Columbia Univ.). [*J. Biol. Chem.*, **167**, 295–6 (1947).]

Choline acetylase was demonstrated in breast, skeletal and cardiac muscle. The amounts were smaller than in brain tissue.

Julia O. Holmes (Chem. Abstr.).

3. Pharmacology and Treatment.

Effect of Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) on Permeability of Meningeal Capillaries. Gelvin, E. Philip, Elias, Herbert, and McGavack, Thomas Hodge (N.Y. Med. Coll., New York, N.Y.). [*J. Pharmacol.*, **89**, 101–5 (1947); *cf. C. A.*, **40**, 6665[8].]

Repeated administration of benadryl to hospital patients with various disorders caused no change in the permeability of the meningeal capillaries to fluorescein and no significant change in the chemistry, cytology, pressure, or dynamics of the spinal fluid.

L. E. Gilson (Chem. Abstr.).

Mechanism of the Action of Calcium by Suboccipital and Intravenous Administration. Amiragova, M. G. (Shtern Inst. of Physiol., Moscow). [*Byull. Eksptl. Biol. Med.*, **21**, *No.* 4, 53–6 (1946).]

On intracranial and on intravenous administration of Ca in dogs there is a liberation in the cerebrospinal fluid and in the blood of a substance of sympathomimetic character. In the study of the metabolism of the vegetative centers it is necessary to use the blood obtained from the sinus through the torcular Herophili.

H. A. Wegner (Chem. Abstr.).

Pharmacological Action of Dibenzylmethylamine (566 *Labaz*). *Heymans, C., Dallemagne, M. J., and Bacq, Z. M. (Univ. Gand, Belgium).* [*Arch. intern. pharmacodynamie*, **72**, 233–48 (1946).]

Dibenzylmethylamine is not sympathomimetic, but sensitizes the animal to adrenaline and to hypertensive reflexes of sinocarotid origin. It is a diuretic, and stimulates respiration centrally. It is a very active stimulant for the psychic and motor cerebral centers. It is a powerful local anesthetic, but causes much local edema, and so is unsuitable for surgical use.

M. L. C. Bernheim (Chem. Abstr.).

Action of Prostigmine, Eserine, Diisopropyl Fluorophosphate and Atropine on the Central and Peripheral Transmission of Nerve Impulses. Heymans, C., Pannier, R., and Verbeke, R. (Univ. Gand, Belgium). [*Arch. intern. pharmacodynamie*, **72**, 405–29 (1946).]

Prostigmine, eserine, diisopropyl fluorophosphate and atropine injected into a dog head by means of the crossed-circulation technique do not modify the reflex or direct excitability of the respiratory or cardiovascular centers. Diisopropyl fluorophosphate sensitizes these centers to the action of eserine and prostigmine.

M. L. C. Bernheim (Chem. Abstr.).

A New Pharmacological Action of Cocaine. Anticonvulsant Action. Gutierrez-Noriega, C., and Zapata Ortiz, V. (Inst. nacl. higiene salud publica, Lima). [*Rev. med. exptl.* (*Peru*), **4**, 59–100 (1945).]

Subconvulsive doses of cocaine were antagonistic to metrazole in dogs, mice and guinea-pigs. A similar antagonism to strychnine was observed with mice

and in certain chloralosed dogs, but not with unanesthetized dogs. In curarized dogs there was no synergism or antagonism in hypertensive reactions, but in many cases cocaine abolished the hypertensive reactions associated with metrazole convulsions. H. L. Williams (Chem. Abstr.).

Role of the Sympathetic Nervous System in Changes of Subordinate Conditions in the Central Nervous System Under the Action of Morphine. Zukusov, V. V. [*Farmakol. i Toksikol.*, **9**, *No.* 1, 8–12 (1946).]

The influence of morphine (I) on summation of impulses was tested in rabbits after extirpation of the superior cervical ganglia. Electric impulses were employed at 0·5, 1 and 2 v. They were intensified by injecting adrenaline (II), pervitin (III), benzedrine (IV), ephedrine (V), or sympathol (VI) into an ear vein. Extirpation of the ganglia increased the capacity of the central nervous system to summate impulses, and decreased the constancy of the effect of (I) on summation. Sympathomimetic amines tend to restore the lost summation capacity. This effect is parallel to the relative activity of the drug as a stimulant to the central nervous system. The effect of (I) is indirect, not through the sympathetic nervous system. Urethan has a similar effect. The intensification activity of the tested amines is indicated by the dose, per kgm. of body weight, for impulses of 1 v., as follows: (II), 5; (III), 0·0001; (IV), 0·0003; (V), 0·0025; (VI), 0·006 (unit not stated). Julian F. Smith (Chem. Abstr.).

The Effect of Benzedrine on Mental or Physical Fatigue in Soldiers. Somerville, Walter (*Exptl. Sta., Suffield, Alberta*). [*Can. Med. Assoc. J.*, **55**, 470–6 (1946).]

Benzedrine in 15 mgm. doses over a period of 17 hours did not significantly enable 50 soldiers to return better performances over an obstacle course than did placebo pills; nor did 35 mgm. show any appreciable effect in the last 24 hours of a 56-hour physically fatiguing exercise on 50 subjects. When given to 73 officers in 40 mgm. doses in the last 34 hours of a 72-hour test on staff problems, no significant effect was shown over inert control substances. There was no evidence that benzedrine tended to prevent sleep. No side effects of any significance were noted. G. H. W. Lucas (Chem. Abstr.).

A Comparison of Amphetamine Sulfate with Other Stimulants of the Central Nervous System in Morphine Respiratory Depression. Handley, Carroll A., and Ensberg, Dorrence L. (*Baylor Univ. Coll. Med., Houston, Texas*). [*Anesthesiology*, **6**, 561–4 (1945).]

The results of this study on 14 human subjects indicate that amphetamine sulfate is the most effective drug of the 5 stimulants studied in antagonizing morphine respiratory depression. Amphetamine is also more prompt in acting than the other 4 agents. Average percentage increases in minute volume above the depressed levels were as follows: Amphetamine 102, nikethamide 37, ephedrine 30, metrazole 21, and caffeine 17 per cent. Ruth Berggren (Chem. Abstr.).

A New Lethal Dose of Curare, with Some Observations on the Pathology Produced by Large Doses. Cole, Frank (*Univ. of Minnesota, Minneapolis*). [*Anesthesiology*, **7**, 190–7 (1946).]

The anoxic lethal dose of intocostrin in the dog is 0·065 c.c. per lb. body weight. The anoxic lethal dose is unaffected by cyclopropane-O anesthesia. The death of one dog after administration of a sublethal dose indicates the possibility of a cumulative effect of curare. The use of curare on succeeding days may be associated with a heightened effect of the drug. An unidentified anti-curare effect was encountered with a technique including tracheal intubation, cyclopropane-O anesthesia, pentothal induction, and the administration of the curare with saline solution through rubber tubing. The deaths of 2 dogs show that the animal is in a dangerous condition on emergence from deep curarization. There is a nonanoxic lethal dose of curare. Dogs can make complete recoveries, with artificial respiration, after receiving 0·33 c.c. intocostrin per lb. body weight. The lethal dose of intocostrin in dogs, in the presence of continuous artificial respiration is about

20 times the anoxic lethal dose. Large doses of curare appear to affect the cardiovascular system. No clinical evidence of brain damage could be found (other than that due to anoxia) attributable to large doses of curare. Bloody diarrhoea was a constant finding in the later experiments. Prostigmine does not appear to be a perfect neutralizing agent for large doses of curare. The safest and proper method of terminating the effects of a very large dose of curare is continuous artificial respiration until the animal has recovered completely.

RUTH BERGGREN (Chem. Abstr.).

Antagonism Between Sulfanilamide and Certain Vitamins with Respect to the Nervous System of the Rat. Lecoq, Raoul, Chauchard, Paul, and Mazoue, Henriette (Sorbonne, Paris). [*Compt. rend. soc. biol.*, **140**, 279–80 (1946).]

Daily injection of sulfanilamide prolonged nerve chronaxia and shortened muscle chronaxia. These changes are similar to those seen in chronic alkalosis and they were prevented by administration of *p*-aminobenzoic acid, nicotinic acid, riboflavin, or ascorbic acid. They were not modified by thiamine, adenine, pantothenic acid, or pyridoxine. L. E. GILSON (Chem. Abstr.).

Potassium versus Biotin in the Treatment of Progressive Paralysis in Dogs. Smith, Susan Gower (Duke Univ., Durham, N.C.). [*Proc. Soc. Exptl. Biol. Med.*, **63**, 339–41 (1946).]

In the paralysis previously described (*C. A.*, **39**, 5300[8]) restoration of K to the diet causes a return to a nearly normal state. Biotin is less effective; it appears to work indirectly, possibly by mobilizing K temporarily or having a synergistic effect when the K reserves are too low to operate alone.

L. E. GILSON (Chem. Abstr.).

The Mode of Action of Anticonvulsant Drugs on Electrically Induced Convulsions in the Rabbit. Barany, E. H., and Stein-Jensen, D. [*Arch. intern. pharmacodynamie*, **73**, 1–47 (1946).]

The convulsive threshold, seizure-pattern and post-convulsive stupor were studied in rabbits stimulated by short periods of 50-cycle a.c. With stimulus duration of 0·21, 1·0, and 4·0 second, the thresholds are 58, 28 and 23 milliamp. Variations of 10 per cent. in the threshold may occur. After a convulsion, the threshold returns to normal in about 1 hour, and it rises slightly after repeated convulsions. Phenobarbital, phenytoin, barbital, and bromide influence the threshold much more with 0·21 second than with 1·0 second, Na phenobarbital (10 mgm./kgm.) raises the threshold 96 per cent. at 0·21 second, but only 25 per cent at 1·0-second stimulation. All the drugs shorten the tonic phase of threshold convulsions, and usually shorten the total duration of the fit, and often atypical fits occur. The seizure-pattern, in normal rabbits, is independent of the stimulus duration and intensity. The tonic phase lasts about 15 seconds and the clonic about 4 seconds. After the drugs, the pattern is dependent on the stimulus. The duration of the post-convulsive stupor is reduced by phenytoin but not by the other drugs.

The Influence of the Electrode Arrangement in the Determination of Drug Action by Means of Electrical Convulsive Thresholds. Barany, E. H. [*Ibid.*, 189–92.]

Na phenobarbital (10 mgm./kgm.) causes a greater rise in the convulsive threshold if the test current is applied through electrodes in the conjunctival sacs rather than in the external auditory duets. M. L. C. BERNHEIM (Chem. Abstr.).

Action of Diallylbarbituric Acid (Dial) on the Electrically Induced Epileptic Fit. Barany, Ernst H., and Stein-Jensen, Erna (Univ. Upsala, Sweden). [*Acta Pharmacol. Toxicol.*, **2**, 264–7 (1946) (*in English*).

In rabbits, dial had a significant threshold-raising action when a 0·21 second electric stimulus was used, but not when the stimulus was prolonged to 1 second. The total duration of the convulsive seizure was shortened by dial.

L. E. GILSON (Chem. Abstr.).

Action of Narcotics of the Barbituric Acid Group on the Course of Insulin Hypoglycemia. Andreeva, M. P. [*Byull. Eksptl. Biol. Med.*, **14**, *No.* 9, 45–7 (1942).]

Dial and medinal definitely alter the course of insulin-caused hypoglycemia. The symptoms of hypoglycemia are delayed and by the use of fractional introduction of medinal it is possible to reach a complete absence of convulsions, although the blood sugar drops sharply in the meantime. Finally, under such conditions, one dog failed to die, although its blood sugar was kept as low as 16 mgm. per cent. for 6 hours. G. M. Kosolapoff (Chem. Abstr.).

Effect of Some Barbiturates on Tissue Cultures in vitro. *Pomerat, C. M., Drager, G. A., and Painter, J. T.* (*Univ. of Texas, Galveston*). [*Proc. Soc. Exptl. Biol. Med.*, **63**, 322–5 (1946).]

The technique of using hanging-drop tissue cultures of spinal cord taken from chick embryos on the 9th day of incubation for testing the inhibitory action of barbiturates on the outgrowth of nerve fibers is described. Total inhibition was obtained at 1 : 6400 concentration for seconal-Na and at 1 : 3200 for pentobarbital-Na and amytal-Na. For 14 other barbiturates the inhibiting concentrations ranged from 1 : 12,800 to 1 : 800. Fibroblast outgrowth from chick heart fragments *in vitro* was more resistant to barbiturates than fiber outgrowths from cord explants.
L. E. Gilson (Chem. Abstr.).

Distribution of Barbiturates in the Human Body. Andrew, R. L., and Neubauer, L. G. (*Dominion Lab., Wellington, New Zealand*). [*Analyst*, **72**, 21–2 (1947).]

Analyses during over 20 years show that barbital, and phenobarbital are distributed quite uniformly in the liver, brain, kidney, lungs, intestine and thigh muscles, but may be considerably higher in the contents of the stomach and in the urine. W. T. Hall (Chem. Abstr.).

Chloroethylidene-methylene Narcosis. Rossiiskii, D. M. [*Byull. Eksptl. Biol. Med.*, **14**, *No.* 9, 36–45 (1942).]

Experimental narcosis with methylene chloride and ethylidene chloride were performed, on a qualitative basis, in comparison with $CHCl_3$ on dogs. Both substances are tolerated better than $CHCl_3$ and have a lesser period of excitation blood pressure and respiration during narcosis are not noticeably decreased. Numerous human cases are cited in which these substances and mixtures were used in a variety of operations with successful results.
G. M. Kosolapoff (Chem. Abstr.).

Blood Sugar and Pulse Reaction in Therapeutic Shock and in Experimental Increase of Affect. Wohlfahrt, Snorre (*Beckomberga Hosp., Stockholm, Sweden*). [*Monatsschr. Psychiat. Neurol.*, **108**, 121–56 (1943).]

Blood-sugar concentration (I) and pulse rate (II) were determined 30, 15, and 5 to 1 minute before, and 2, 5, 10, 20 to 25, 30, 40, 50, 60 and 70 minutes after, shock induced by metrazole (III), anoxia (N breathing) (IV), or electric stimulation (V). After maximum (III) shock (4 cases) (I) rose by about 75 mgm. per cent. and after usual (III) shock (3 cases) by about 25 mgm. per cent. The time at which the maximum (I) was reached varied from 5 to 60 minutes. When no shock (3 cases) followed (III), (I) did not change significantly, although (II) increased as much as when shock occurred. After (IV) shock (12 cases) (I) rose 9–52 mgm. per cent. The maximum was reached 5–20 minutes after the shock. There was no relation between amount of rise in (I) and intensity of shock or change in (II). After (V) shock (11 cases) (I) rose 21 to 44 mgm. per cent. ; the maximum was reached at 5 to 50 minutes. There was no evident relationship between increases in (I) and (II). Nine patients accustomed to and expecting (III) shock were given 0·9 per cent. NaCl solution instead. (I) rose 9 to 34 mgm. per cent. with the largest increases in the patients showing the strongest affect. (II) also rose sharply in most instances. As controls 20 patients received a NaCl solution injection without any suggestion that it would cause shock. The average increase in (I) was 5 mgm. per cent. and the average (II) decreased.
Warren M. Sperry (Chem. Abstr.).

The Brain Changes Associated with Electrical Shock Treatment: A Critical Review. [*J. Lancet*, **66**, 363–9 (1946).]

That brain changes follow electrical shock treatment seems evident from a review of the literature, but it has not been proved whether they are transitory or permanent. Other complications make estimation difficult, but scattered cell loss and cell changes have been observed in experimental animals and to a less degree in man. The author believes this therapy should be used judiciously and sparingly and only in cases which can definitely profit from its application.

F. A. Cooksley (Psychol. Abstr.).

The Effect of Electric Shock on the Cerebrospinal Fluid. Finkelstein, B. A., and Loewenthal, M. (*County Health Inst., Konigsfeld, Switz.*). [*Monatsschr. Psychiat. Neurol.*, **107**, 315–24 (1943).]

Sugar, chloride, total protein, and the gold-sol and several other reactions were determined in the spinal fluids of 9 patients 3 to 5 minutes after electric shock, and in one patient 20 minutes after an epileptic seizure. No significant deviations from normal were observed. Warren M. Sperry (Chem. Abstr.).

The Action of Carbon Dioxide in Experimental Convulsions. Ozorio de Almeida, Miguel. [*Bull. acad. med.*, **130**, 365–7 (1946).]

The addition of CO_2 to the respiratory air causes disappearance of attacks of various forms of experimental epilepsy produced by the local application of strychnine to the motor cortex. The effect is directly on the motor centers and does not depend on changes in the pH. A. E. Meyer (Chem. Abstr.).

Humoral Changes During Electro-shock Epilepsy in the Curarized Animal. Soulairac, Andre (*Univ. Paris*). [*Compt. rend. soc. biol.*, **140**, 263–4 (1946).]

The hyperglucemia and decrease in alkali reserve produced by electric shock treatment cannot be due entirely to the intense muscular activity commonly provoked, since they are also produced by electric shock in rabbits paralyzed with curare or narcotized with $MgSO_4$. L. E. Gilson (Chem. Abstr.).

Duration of Action of Metrazole. Carlsson, Arvid, and Theander, Georg (*Univ. of Lund, Sweden*). [*Acta Pharmacol. Toxicol.*, **2**, 227–34 (1946) (*in English*).]

The duration of action of a single dose of metrazole (I) was determined in guinea-pigs with the aid of N_2O. After administration of Na diethylbarbiturate plus (I) a higher partial pressure of N_2O is required to obtain a certain degree of narcosis than after the barbiturate alone. This analeptic action against the barbiturate of a single subcutaneous dose of 150 mgm./kgm. of (I) persisted for more than 10 hours after the injection. (I) does not exert an analeptic action against N_2O.

A Depressant Component in the Action of Metrazole. [*Ibid.*, 268–74.]

In tadpoles and frogs the stimulant action of metrazole (I) is followed by depression. (I) appears to act as a depressant in guinea-pigs narcotized with N_2O. Repeated subcutaneous injections of (I) in doses of 35 mgm./kgm. produce convulsions at first, but if continued, have less and less effect (in both rabbits and guinea-pigs). This development of tolerance may indicate a secondary depressant action. L. E. Gilson (Chem. Abstr.).

Analeptics. Jacques, Andre (*Hotel-Dieu de Quebec, Quebec, Can.*). [*Laval Med.*, **11**, 760–82 (1946).]

A review, including caffeine, strychnine, lobeline, coramine, metrazole, picrotoxin, ephedrine, adrenaline, neosynephrine, paredrine, benzedrine, cobefrin, methedrine. H. L. Williams (Chem. Abstr.).

Stimulant and Depressant Effects of Metrazole in Sodium Diethylbarbiturate Depression. Carlsson, Arvid, and Theander, Georg (*Univ. Lund, Sweden*). [*Acta Pharmacol. Toxicol.*, **2**, 379–82 (1946) (*in English*).]

In guinea-pigs depressed with Na diethylbarbiturate the analeptic action of graded doses of metrazole appears to increase only up to a certain limit. Further increase in dosage sometimes results in a reduction of the analeptic effect.

L. E. Gilson (Chem. Abstr.).

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(R.) indicates a *Review*; the title of the book reviewed is followed by the author's name, thus: "Psycho-analysis and its Derivatives, by H. Crichton-Miller (R.)."

(E.) indicates the *Epitome* section; the title of the abstract is followed by the author's name, thus: "Age and human ability. Miles, W. R. (E.)."

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